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La 1^ linea terapeutica nei pazienti senza mutazioni target: lo scenario è cambiato?

Luca Toschi, MD
Medical Oncology
Humanitas Cancer Center

Desenzano, 13 Marzo 2017

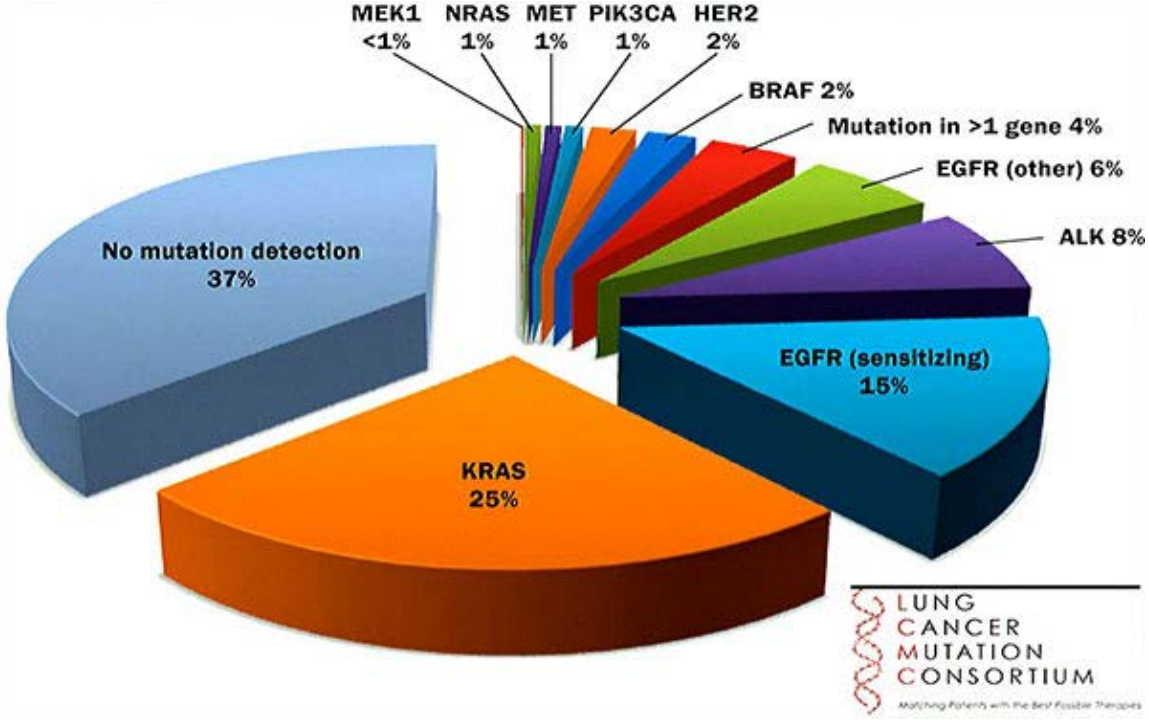
Who are non-oncogene addicted NSCLC?

Lung Cancer Consortium Mutation

- 16 US cancer centers

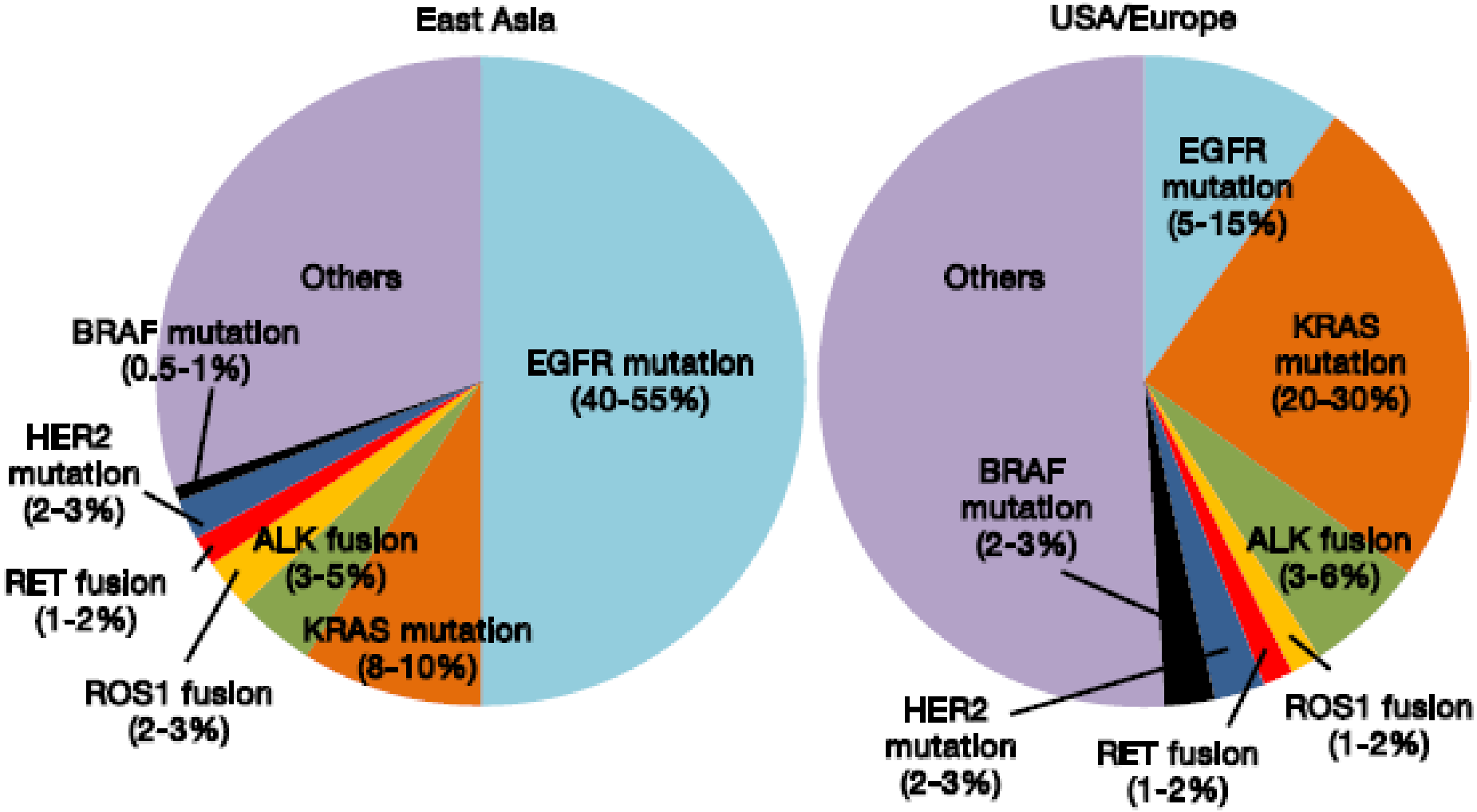
- Test 10 driver mutations in 1007 lung adenocarcinomas

- 37%: no oncogenic driver



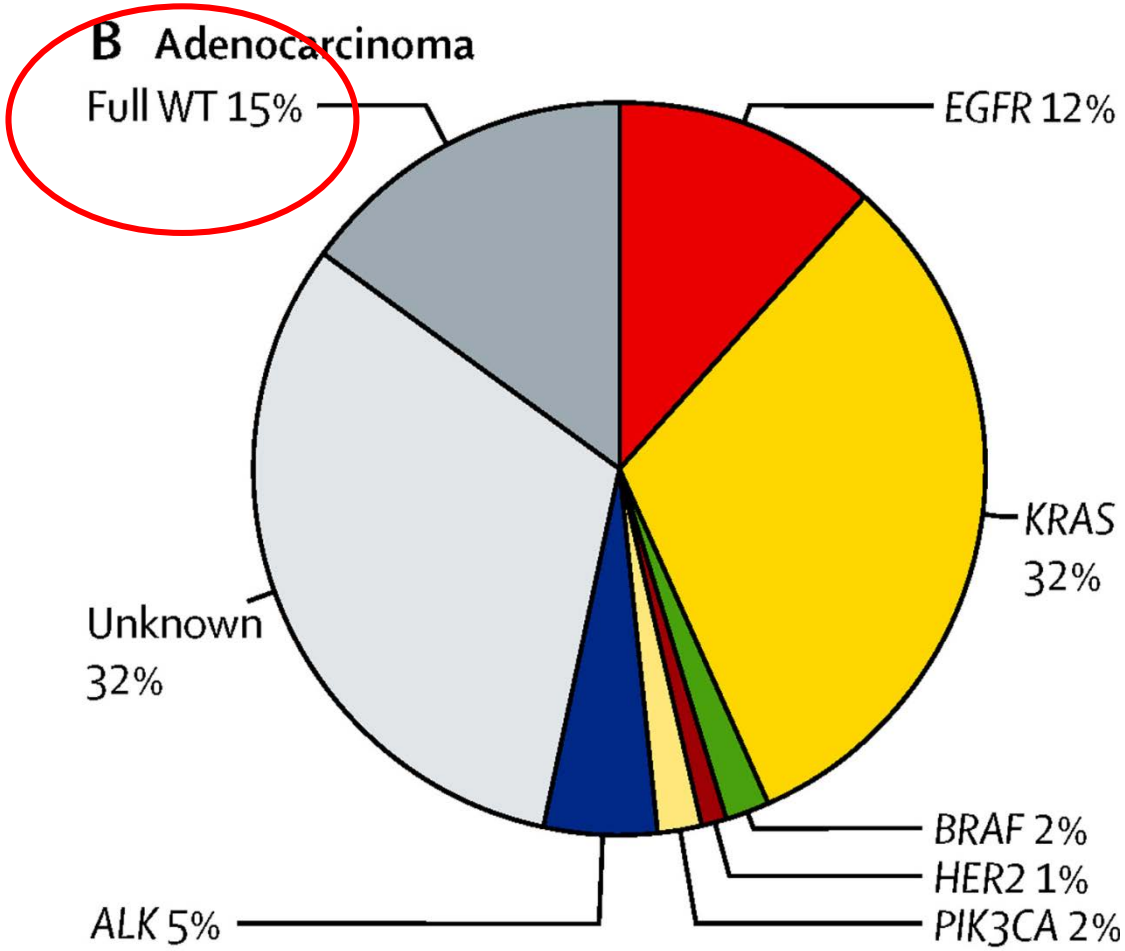
Kris, JAMA 2014

Oncogenic drivers in lung adenocarcinoma



Kohno, TLCR 2015

IFCT: routine molecular profiling of patients with advanced NSCLC

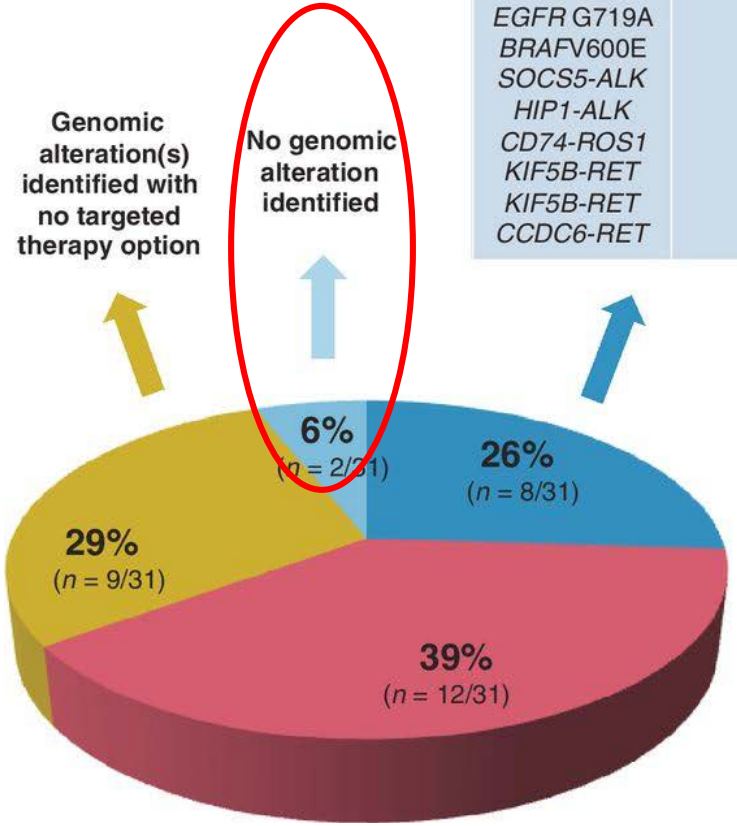


- 28 certified regional genetics centers
- N=17664 NSCLCs
- 6 molecular alterations
- Only 3% enrolled in clinical trials

Barlesi, Lancet 2016

NGS in never/light smokers with lung ADC with negative non-NGS tests

Genomic alteration with targeted therapy in NCCN guidelines	Tumor from same procedure as tumor subjected to non-NGS testing	Patient's clinical course
EGFR G719A	Yes	Recently started erlotinib, response evaluation pending
*BRAF*V600E	Yes	Subsequently passed away
SOCS5-ALK	Yes	**Disease shrinkage (<30%) with crizotinib**
HIP1-ALK	Yes	**Partial response to crizotinib**
CD74-ROS1	Yes	Recently started crizotinib, response evaluation pending
KIF5B-RET	Yes	**Partial response to cabozantinib**
KIF5B-RET	No	**Disease shrinkage (<30%) with cabozantinib**
CCDC6-RET	Yes	Candidate for cabozantinib after progression on chemotherapy



Genomic alteration with targeted agent available on or off a clinical trial	Targeted therapeutic (clinicaltrials.gov number) with potential activity available at institution
CDKN2A loss	CDK4/6 inhibitor (NCT01237236)
EGFR L747P	erlotinib, afatinib
EGFR exon 18 del (*n* = 2)	pan-ERBB inhibitor (NCT01858389)
EGFR exon 20 ins	pan-ERBB inhibitor (NCT01858389)
ERBB2 L755F	pan-ERBB/mTOR inhibitor (NCT01953926)
FGFR1 T141R	FGFR inhibitor (NCT01948297)
KRAS G12C	ERK inhibitor (NCT01781429)
KRAS Q61H	ERK inhibitor (NCT01781429)
MDM2 amp (*n* = 3)	MDM2 inhibitor (NCT01877382)

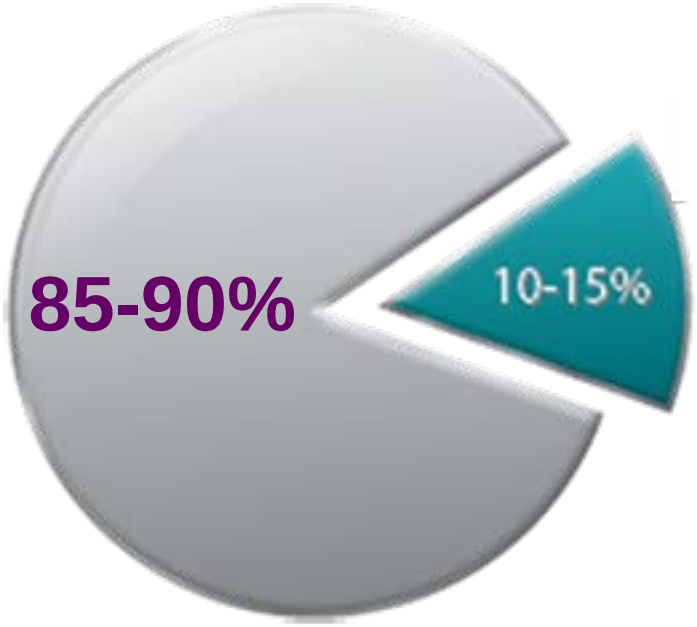
- coding exons of **287** cancer-related genes
- introns of **19** frequently rearranged genes

Drilon, CCR 2015

Today

Who are non-oncogene addicted *untreated* lung adenocarcinomas *in clinical practice?*

EGFR wild type **85-90%**



EGFR-mutant

Linee guida AIOM 2015

In assenza di mutazioni attivanti dell'EGFR, i regimi a due farmaci contenenti platino rappresentano il trattamento standard di prima linea del NSCLC avanzato.

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La 1^ linea terapeutica nei pazienti senza mutazioni target: lo scenario è cambiato?

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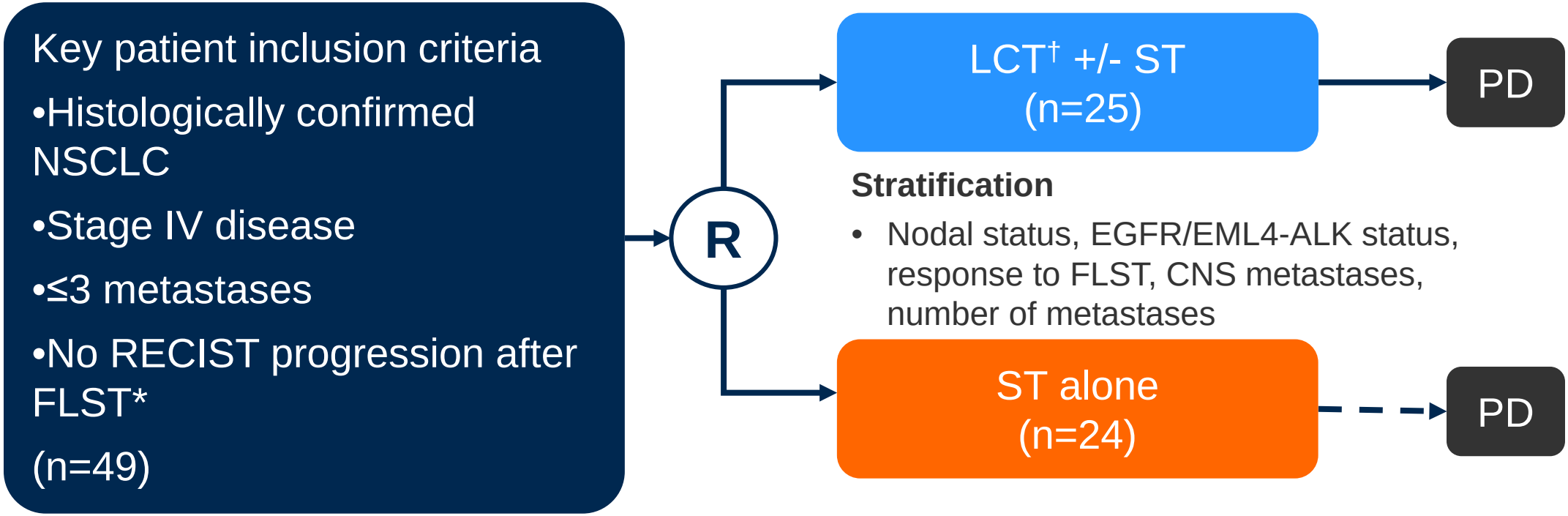
Local consolidative therapy versus maintenance therapy or observation for patients with oligometastatic non-small-cell lung cancer without progression after first-line systemic therapy: a multicentre, randomised, controlled, phase 2 study

Daniel R Gomez, George R Blumenschein Jr, J Jack Lee, Mike Hernandez, Rong Ye, D Ross Camidge, Robert C Doebele, Ferdinandos Skoulidis, Laurie E Gaspar, Don L Gibbons, Jose A Karam, Brian D Kavanagh, Chad Tang, Ritsuko Komaki, Alexander V Louie, David A Palma, Anne S Tsao, Boris Sepesi, William N William, Jianjun Zhang, Qiuling Shi, Xin Shelley Wang, Stephen G Swisher, John V Heymach**

Lancet Oncology 2016

- **Study objective**
  - To investigate the effect of aggressive LCT in patients with oligometastatic NSCLC who did not progress after front-line systemic therapy (FLST)*



Primary endpoint(s)

- PFS

Secondary endpoints

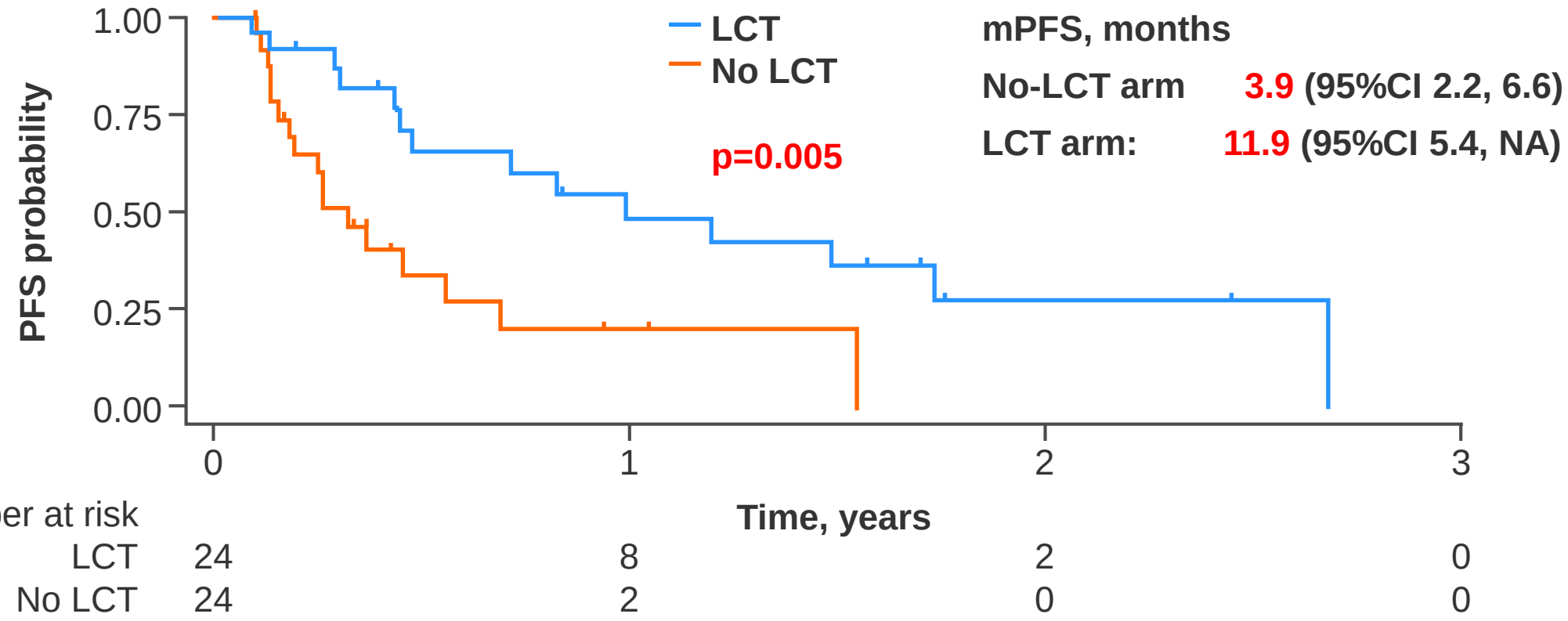
- OS, safety

*≥4 cycles of platinum-doublet chemotherapy, ≥ 3 months of erlotinib, afatinib or gefitinib therapy if EGFR mutation or ≥ 3 months of crizotinib therapy if EML4-ALK fusion; †LCT, local consolidative therapy (i.e. [chemo]radiation or surgical resection of all sites); ST, systemic therapy

Gomez et al. J Clin Oncol 2016; 34 (suppl): abstr 9004

PFS

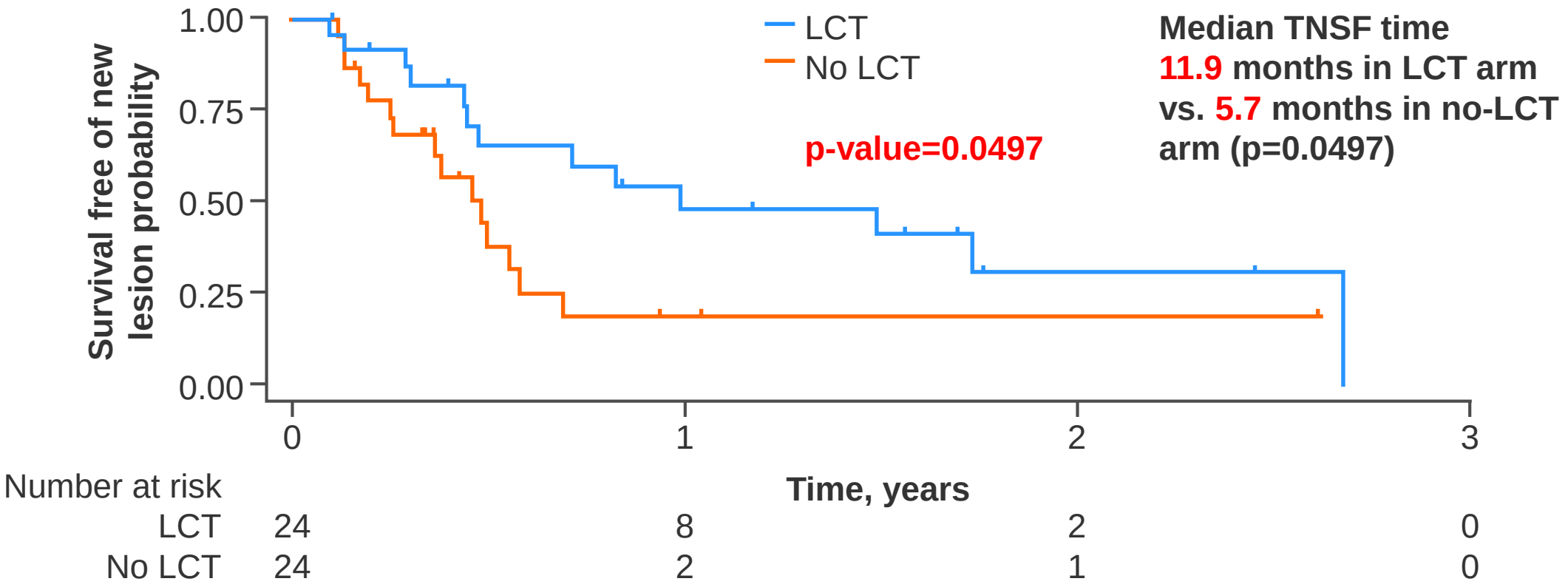
- LCT significantly improved PFS by 8 months and the study was closed early



- No substantial difference in toxicity was observed between the treatment arms
- No grade 3–5 toxicity was observed in the LCT group

Gomez et al. J Clin Oncol 2016; 34 (suppl): abstr 9004

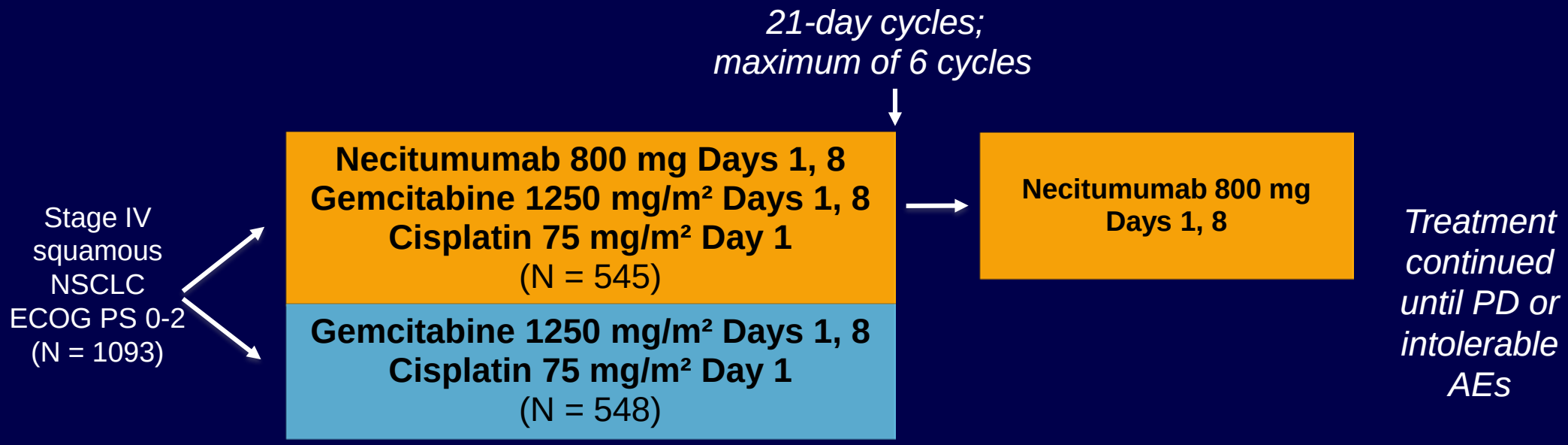
Survival free of new lesions



TNSF, time to new site failure

Gomez et al. J Clin Oncol 2016; 34 (suppl): abstr 9004

SQUIRE: Gemcitabine/Cis + Necitumumab vs Gemcitabine/Cis in Stage IV NSCLC



Radiographic tumor assessment (investigator read): at baseline and every 6 wks until PD

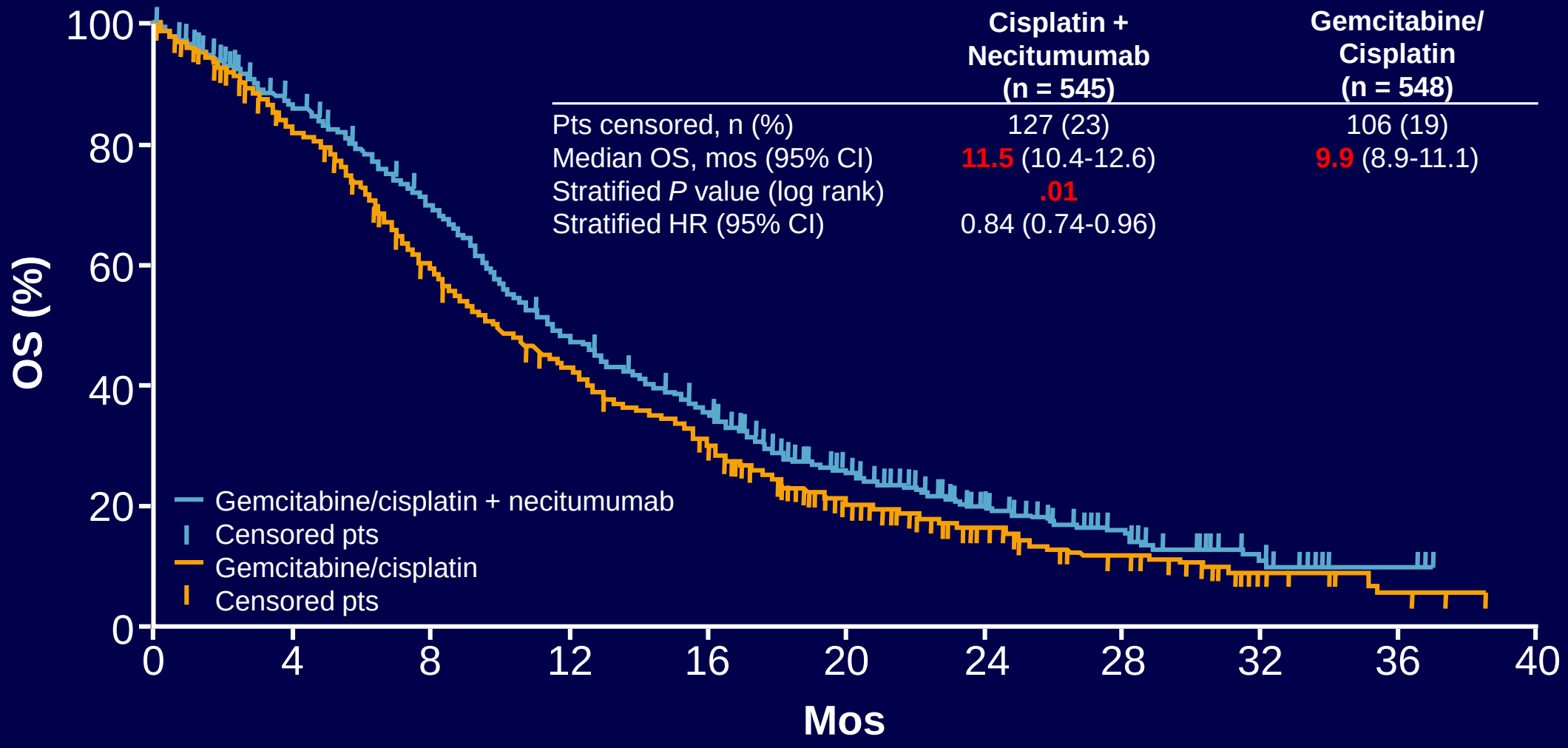
Mandatory tissue collection

- Phase III
- Primary endpoint: OS

Thatcher N, et al. Lancet Oncol. 2015;16:763-774.

Slide credit: clinicaloptions.com

SQUIRE: Overall Survival



	Gemcitabine/ Cisplatin + Necitumumab (n = 545)	Gemcitabine/ Cisplatin (n = 548)
Pts censored, n (%)	127 (23)	106 (19)
Median OS, mos (95% CI)	**11.5** (10.4-12.6)	**9.9** (8.9-11.1)
Stratified *P* value (log rank)	**.01**	
Stratified HR (95% CI)	0.84 (0.74-0.96)	

Thatcher N, et al. Lancet Oncol. 2015;16:763-774.

Slide credit: clinicaloptions.com

SQUIRE: Adverse Events

AEs, %	Gem/Cis + Neci Overall (N = 538)	Gem/Cis Overall (N = 541)
Any AEs	99.1	97.8
▪ Grade ≥ 3 AEs	**72.1**	**61.6**
Serious AEs	47.8	37.5
AEs leading to discontin. of any study drug	**31.2**	**24.6**
AEs with outcome of death*	12.3	10.5
▪ Treatment related death†	2.8	1.8

*Including death due to PD.

†As assessed by investigators; missing relationship was counted as related.

Thatcher N, et al. Lancet Oncol. 2015;16:763-774.
Thatcher N, et al. ASCO 2014. Abstract 8008.

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Necitumumab in squamous cell NSCLC

US	Approved by FDA
EU	Approved by EMA
UK	Not approved by NICE

The committee concluded that necitumumab did not meet the criteria to be considered a life-extending, end-of-life treatment

ImmunOncology: the revenge

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JOURNAL OF CLINICAL ONCOLOGY

ASCO SPECIAL ARTICLE

Clinical Cancer Advances 2016: Annual Report on Progress Against Cancer From the American Society of Clinical Oncology

Advance of the Year: Cancer Immunotherapy

New Treatment Paradigm for Lung Cancer

Dizon, JCO 2016

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JOURNAL OF CLINICAL ONCOLOGY

ASCO SPECIAL ARTICLE

Clinical Cancer Advances 2017: Annual Report on Progress Against Cancer From the American Society of Clinical Oncology

ADVANCE OF THE YEAR: IMMUNOTHERAPY 2.0: EXPANDING USE AND REFINING PATIENT SELECTION

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2009

MAGRIT: The Largest-Ever Phase III Lung Cancer Trial Aims to Establish a Novel Tumor-Specific Approach to Therapy

Preeta Tyagi, Beloo Mirakhur
GlaxoSmithKline Oncology, Collegeville, PA

2014

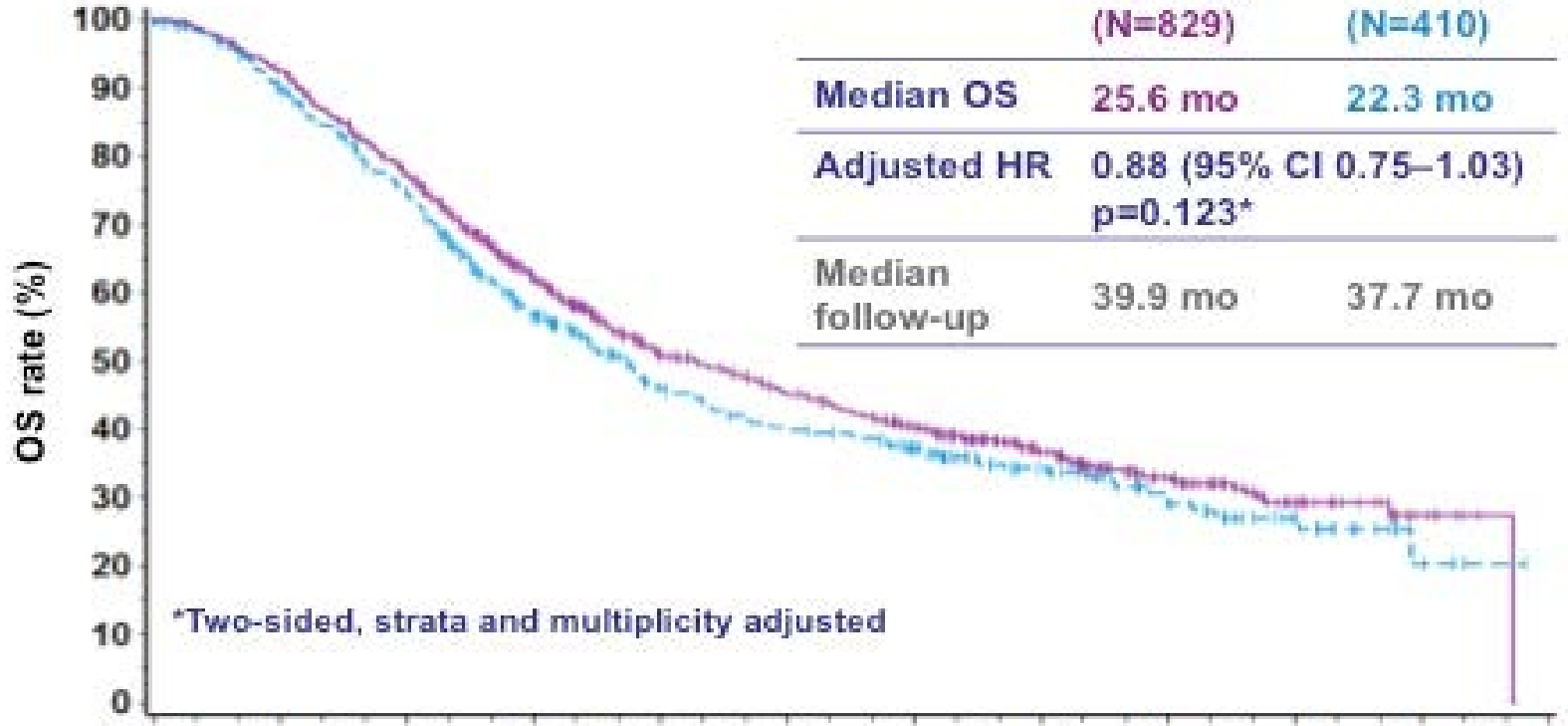
ESMO 2014 Press Release: MAGRIT Phase III Trial Results Raise Questions About the Future of Lung Cancer Vaccination

Experts are divided on the value of lung cancer vaccination after disappointing results from the MAGRIT phase III trial

2013: START trial with tecemotide in NSCLC

Primary endpoint: Overall survival

	L-BLP25 (N=829)	Placebo (N=410)
Median OS	25.6 mo	22.3 mo
Adjusted HR	0.88 (95% CI 0.75–1.03) p=0.123*	
Median follow-up	39.9 mo	37.7 mo



At risk (N)												
Placebo	410	353	285	188	127	108	88	59	33	18	4	0
L-BLP25	829	757	617	429	301	255	204	128	73	33	8	0

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NEJM 2015: 3 articles in 6 months

Nivolumab versus Docetaxel in Advanced Nonsquamous Non-Small-Cell Lung Cancer.

Borghaei H, Paz-Ares L, Horn L, Spigel DR, Steins M, Ready NE, Chow LQ, Vokes EE, Felip E, Holgado E, Barlesi F, Kohlhäufl M, Arrieta O, Burgio MA, Fayette J, Lena H, Poddubskaya E, Gerber DE, Gettinger SN, Rudin CM, Rizvi N, Crinò L, Blumenschein GR Jr, Antonia SJ, Dorange C, Harbison CT, Graf Finckenstein F, Brahmer JR.

N Engl J Med. 2015 Oct 22;373(17):1627-39. doi: 10.1056/NEJMoa1507643. Epub 2015 Sep 27.

PMID: 26412456

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Nivolumab versus Docetaxel in Advanced Squamous-Cell Non-Small-Cell Lung Cancer.

Brahmer J, Reckamp KL, Baas P, Crinò L, Eberhardt WE, Poddubskaya E, Antonia S, Pluzanski A, Vokes EE, Holgado E, Waterhouse D, Ready N, Gainor J, Arén Frontera O, Havel L, Steins M, Garassino MC, Aerts JG, Domine M, Paz-Ares L, Reck M, Baudelet C, Harbison CT, Lestini B, Spigel DR.

N Engl J Med. 2015 Jul 9;373(2):123-35. doi: 10.1056/NEJMoa1504627. Epub 2015 May 31.

PMID: 26028407

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Pembrolizumab for the treatment of non-small-cell lung cancer.

Garon EB, Rizvi NA, Hui R, Leighl N, Balmanoukian AS, Eder JP, Patnaik A, Aggarwal C, Gubens M, Horn L, Carcereny E, Ahn MJ, Felip E, Lee JS, Hellmann MD, Hamid O, Goldman JW, Soria JC, Dolled-Filhart M, Rutledge RZ, Zhang J, Lunceford JK, Rangwala R, Lubiniecki GM, Roach C, Emancipator K, Gandhi L; KEYNOTE-001 Investigators.

N Engl J Med. 2015 May 21;372(21):2018-28. doi: 10.1056/NEJMoa1501824. Epub 2015 Apr 19.

PMID: 25891174

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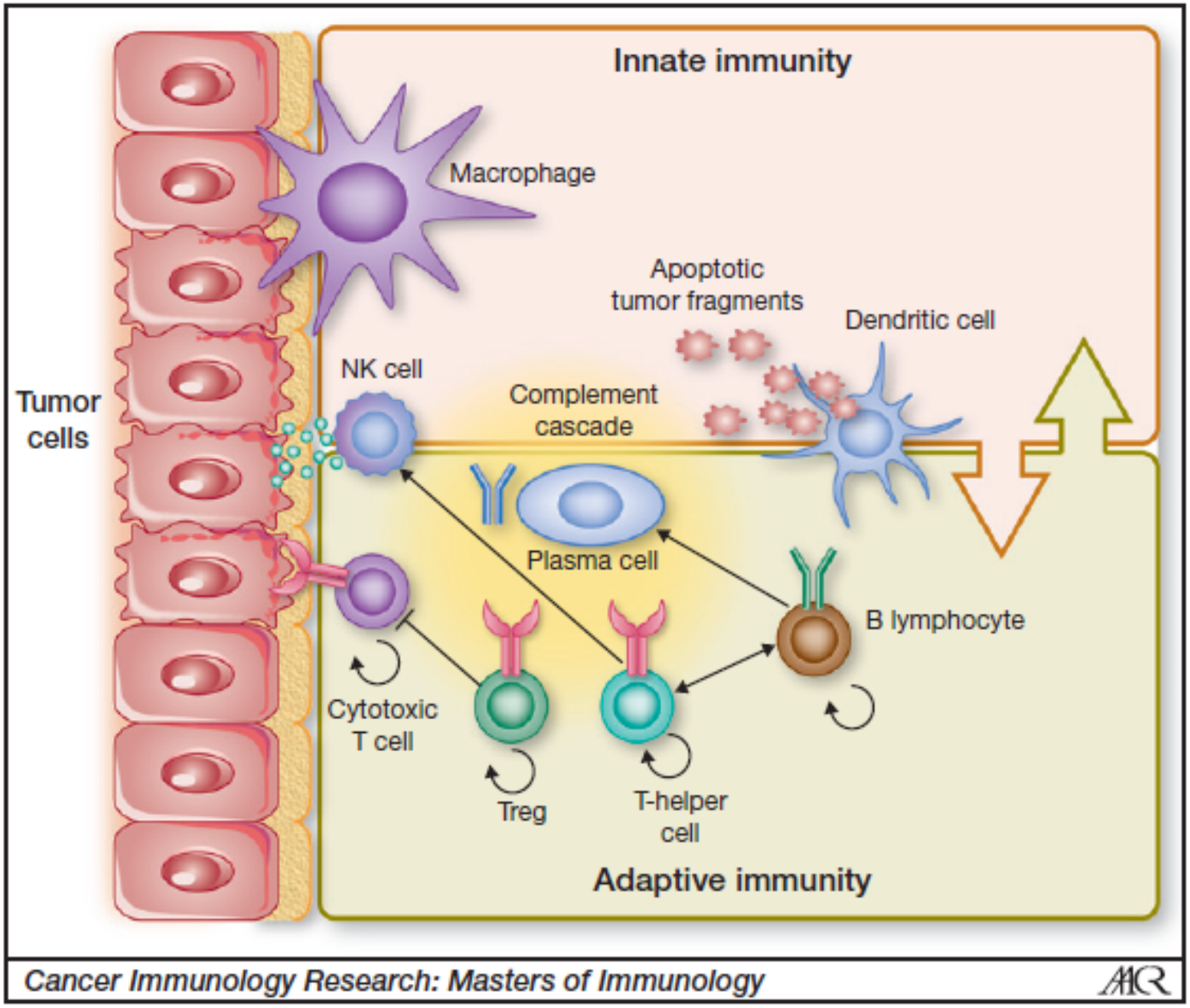
Basic Immunology



Ploegh HL Cancer Immunol Res 1:5-10; 2013

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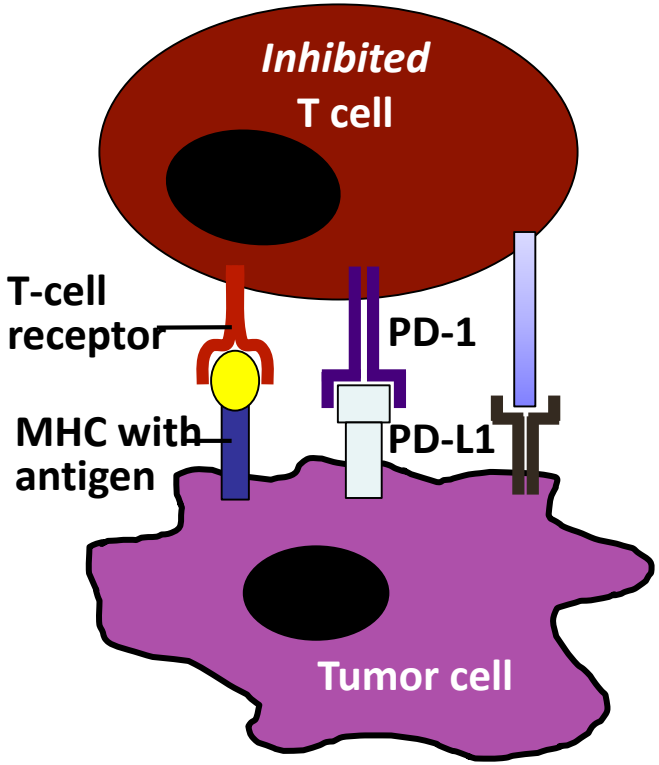
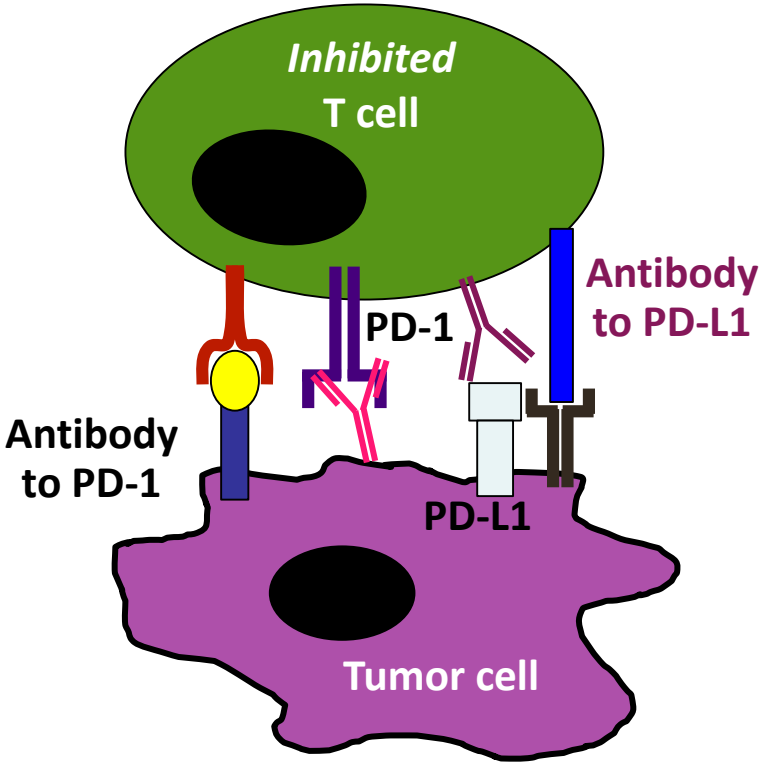
PD-1/PD-L1 in the Immune Response

Binding of PD-L1 to PD-1 receptor downregulates T-cell effector functions



Antibody-mediated blockage of the binding of PD-L1 protein to PD-1 receptor restores T-cell effector functions



Adapted from Sznol M, Chen L. *Clin Cancer Res.* 2013;19:1021-1034

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Randomized 2/3L phase III trials of anti-PD1/PD-L1 agents vs docetaxel

	TRIAL	Drug	Target	PD-L1	RR (%)		PFS (mo.)		OS (mo.)	
					CI	D	CI	D	CI	D
AIFA	CheckMate 017	Nivolumab	PD-1	Any	20	9	3.5	2.8	9.2	6.0
AIFA	CheckMate 057	Nivolumab	PD-1	Any	19	12	2.3	4.2	12.2	9.4
EMA	KEYNOTE 010	Pembrolizumab*	PD-1	Positive	18	9	4.0	4.0	12.7	8.5
FDA	OAK	Atezolizumab	PD-L1	Any	14	13	2.8	4.0	13.8	9.6

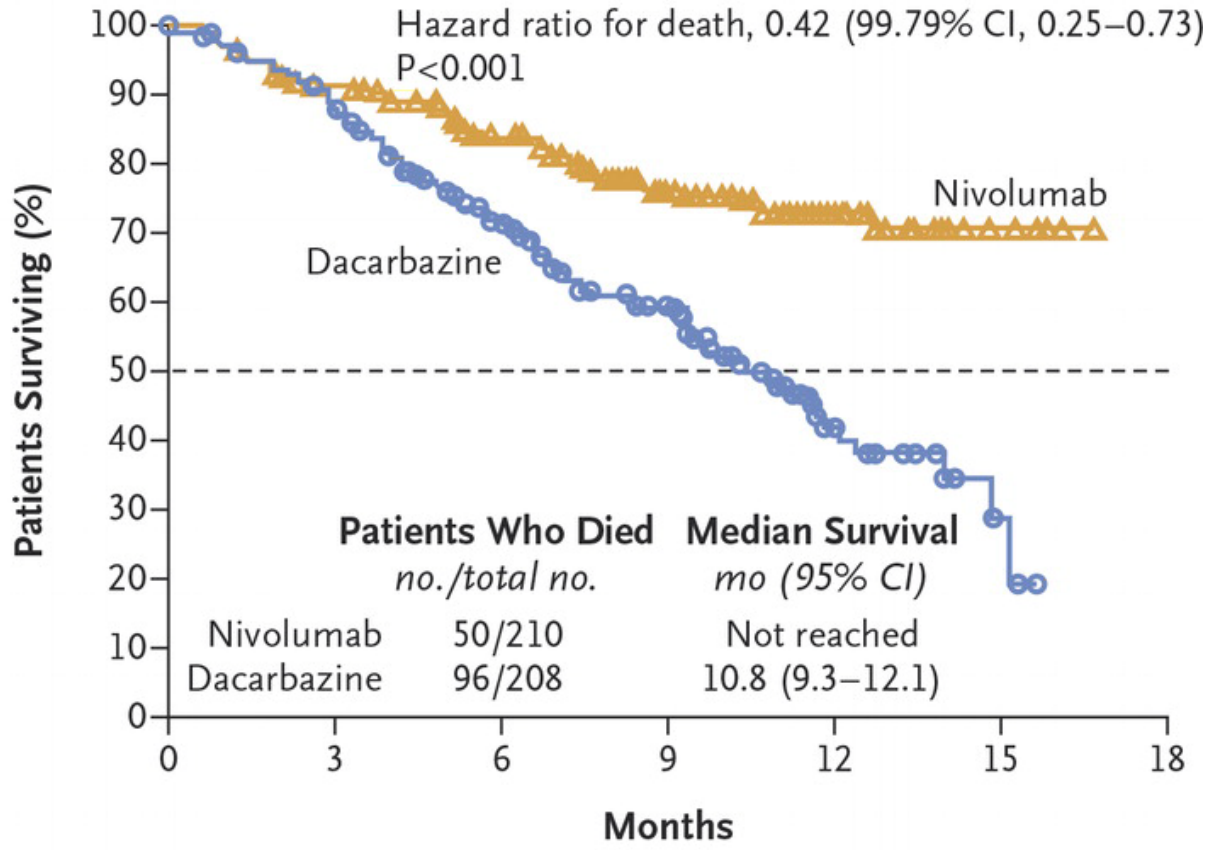
*Data in the table for 10 mg/kg dose

CI: checkpoint inhibitor

D: docetaxel

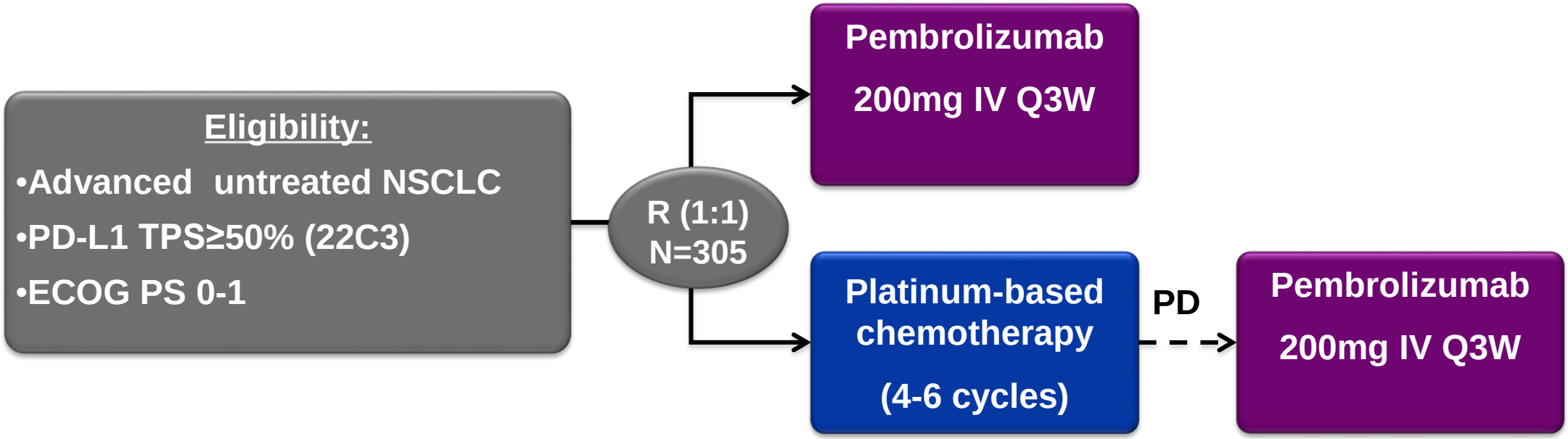
P<.05

Nivolumab vs dacarbazine in advanced melanoma: overall survival



Robert, NEJM 2015

KEYNOTE-024: first line pembrolizumab vs platinum-based CT in PD-L1+ NSCLC



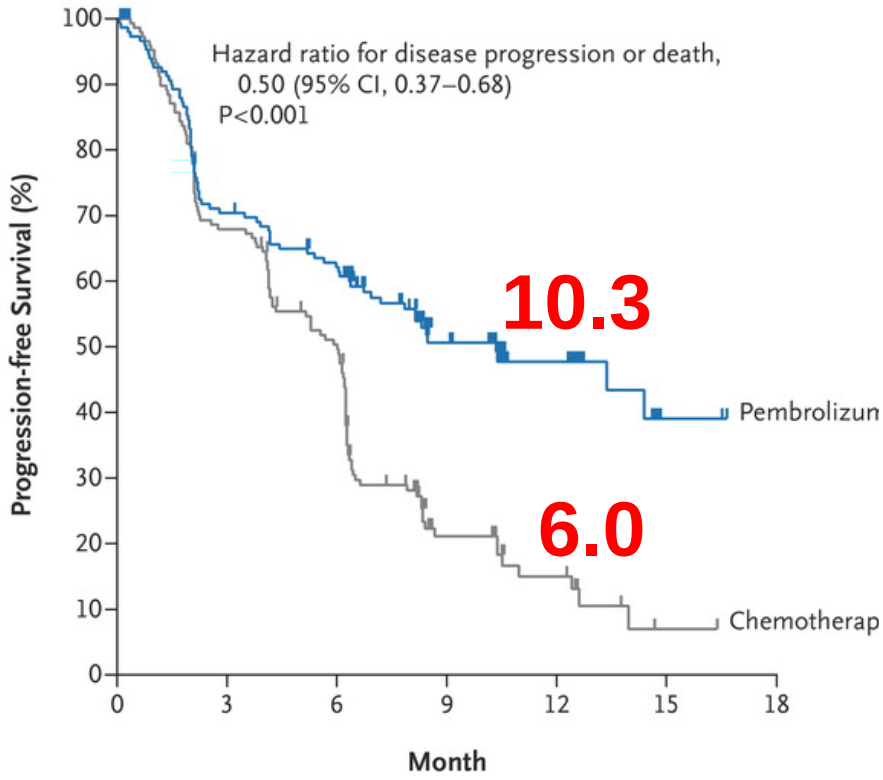
Primary endpoint: PFS

Secondary endpoints: OS, RR, safety

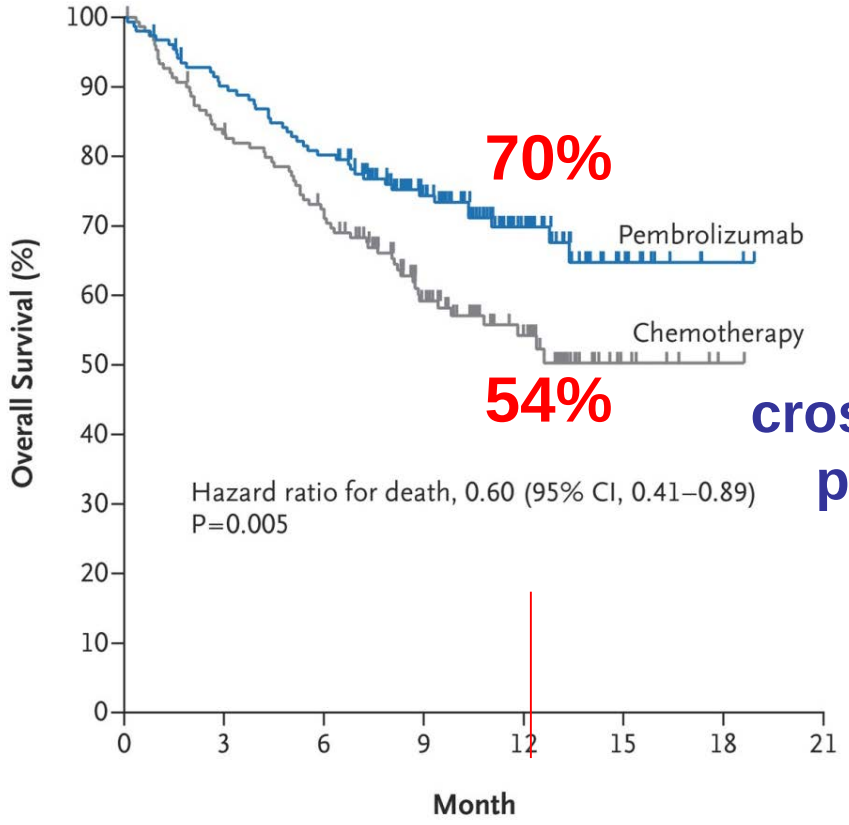
M Reck, et al. ESMO 2016 Abstract LBA8

KEYNOTE-024: PFS and OS

PFS
HR 0.50, p<.001



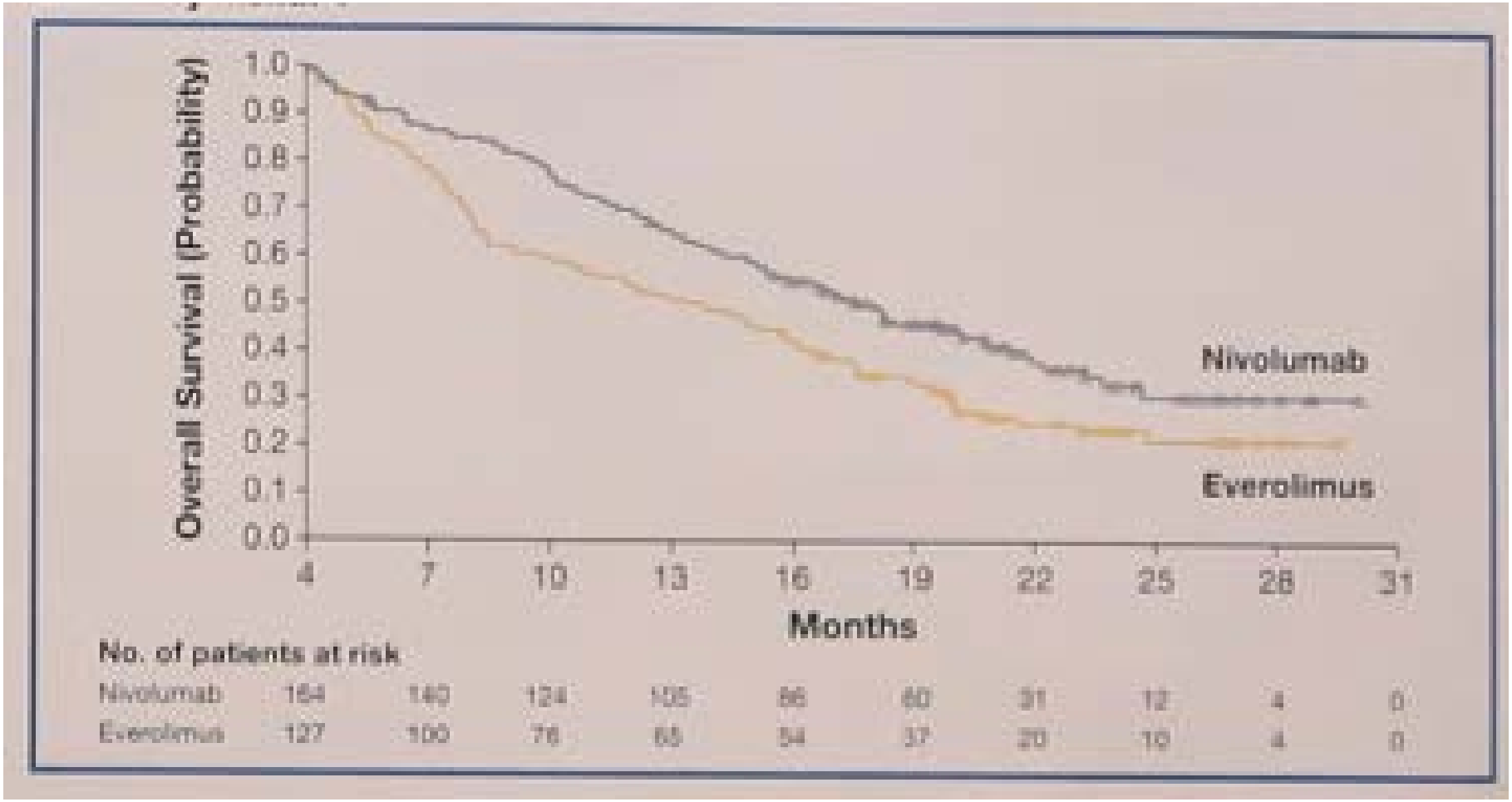
OS
HR 0.60, p=.005



50% crossover to pembro

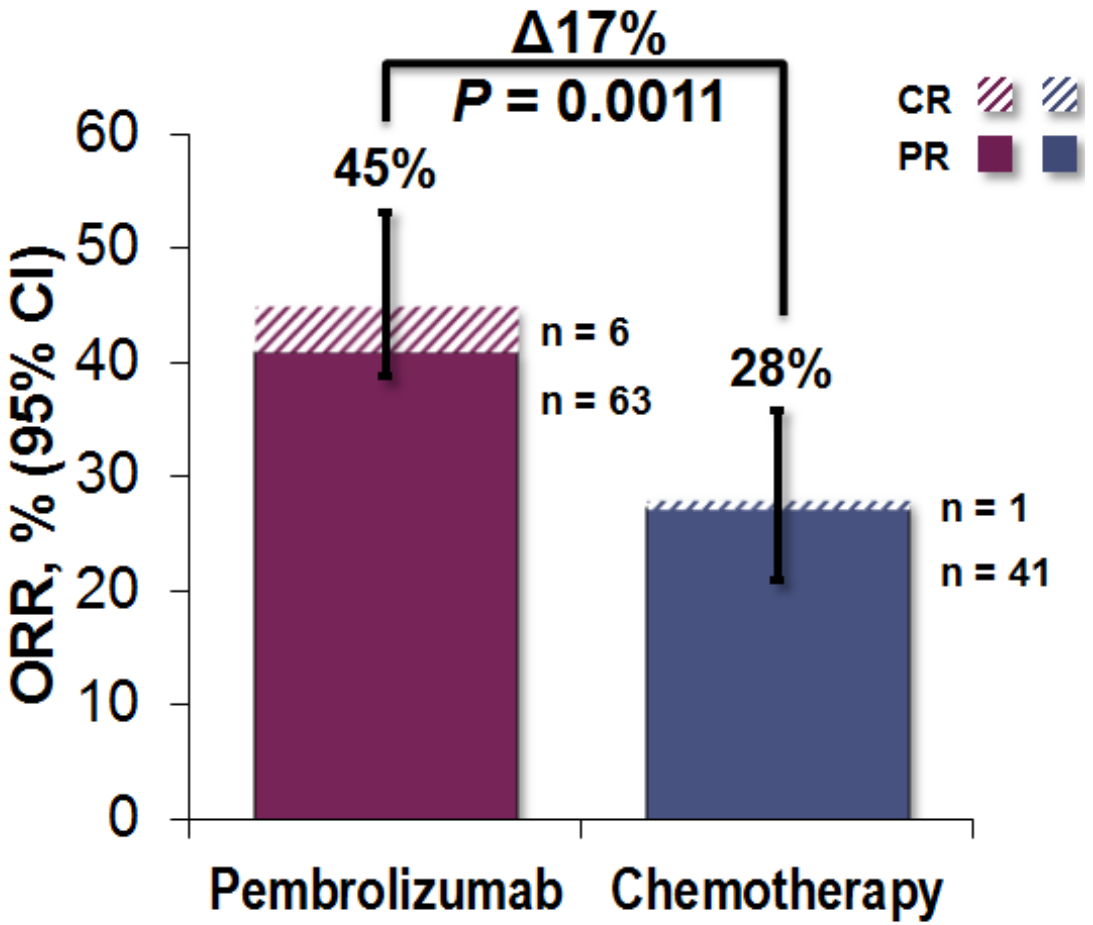
NEJM 2016

OS in renal cell carcinoma patients with PD as best response



Motzer, ASCO 2016

KEYNOTE-024: RR



Reck, ESMO 2016

KEYNOTE-024: Select Treatment-Related Adverse Events

Adverse Event (≥ 10% in Either Arm), %	Pembrolizumab (n = 154)		Chemotherapy (n = 150)	
	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Any	73.4	26.6	90.0	53.3
Nausea	9.7	0	43.3	2.0
Diarrhea	14.3	3.9	13.3	1.3
Vomiting	2.6	0.6	20.0	0.7
Anemia	5.2	1.9	44.0	19.3
Fatigue	10.4	1.3	28.7	3.3
Pyrexia	10.4	0	5.3	0
Neutropenia	0.6	0	22.7	13.3
Thrombocytopenia	0	0	11.3	5.3

Reck M, et al. N Engl J Med. 2016;[Epub ahead of print].

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Pembrolizumab in 1st line PD-L1+ NSCLC

US	Approved by FDA
EU	Approved by EMA
UK	Not approved by NICE

Although there was sufficient evidence that pembrolizumab had an important extension-to-life benefit [..] compared with standard of care, the magnitude of the overall survival gain was uncertain because the data is immature + not cost effective use of NHS resources

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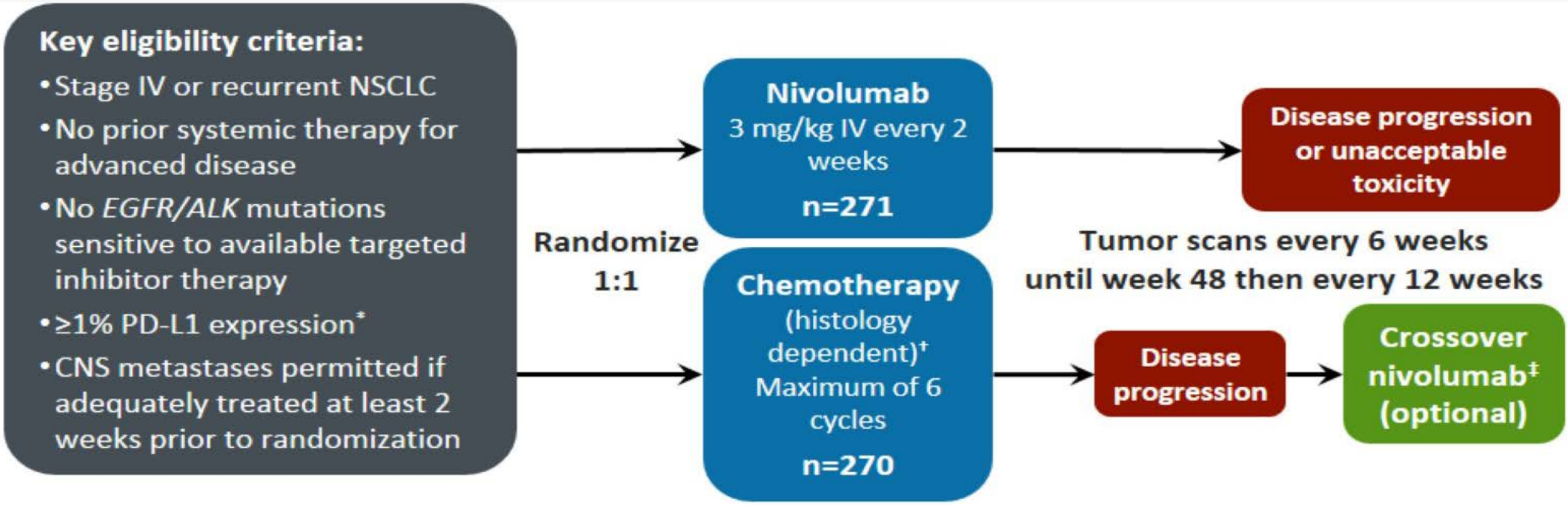
CheckMate-026



*Dako 28-8 validated; archival tumor samples obtained ≤6 months before enrollment were permitted; PD-L1 testing was centralized

†Squamous: gemcitabine 1250 mg/m^2 + cisplatin 75 mg/m^2; gemcitabine 1000 mg/m^2 + carboplatin AUC 5; paclitaxel 200 mg/m^2 + carboplatin AUC 6; nonsquamous: pemetrexed 500 mg/m^2 + cisplatin 75 mg/m^2; pemetrexed 500 mg/m^2 + carboplatin AUC 6; option for pemetrexed maintenance therapy

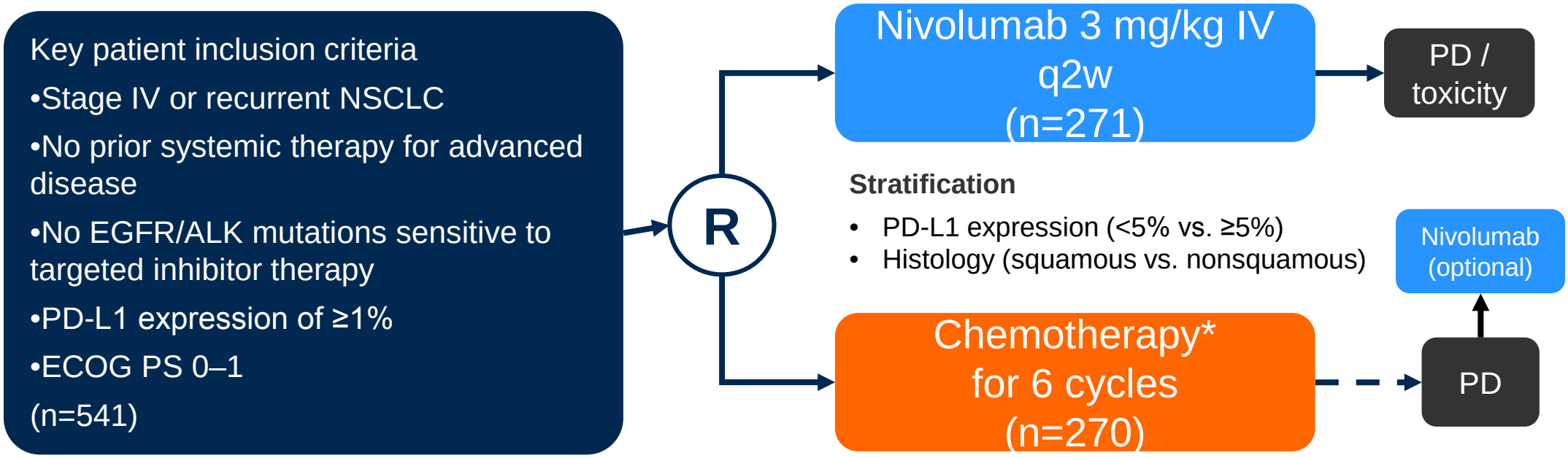
‡No washout required before crossover

ClinicalTrials.gov website.

Medscape EDUCATION

CheckMate-026: 1st line nivolumab vs platinum-based CT in PD-L1+ NSCLC

- **Study objective**
  - To evaluate the efficacy of first-line nivolumab vs. investigator choice of platinum-based doublet chemotherapy in stage IV/recurrent PD-L1-positive NSCLC



Primary endpoint

•PFS (≥5% PD-L1+)

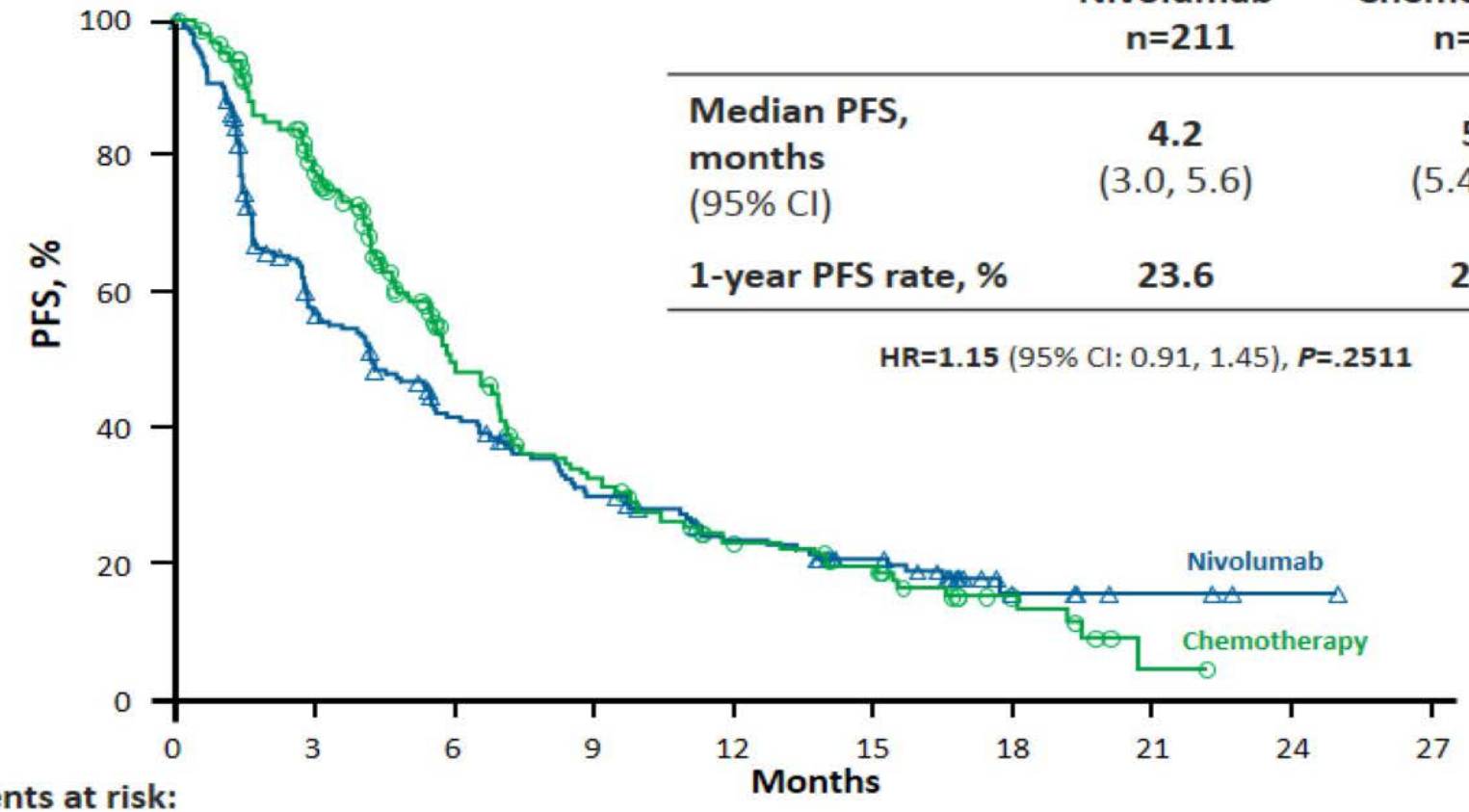
Secondary endpoints

•PFS (≥1% PD-L1+), OS, ORR

*Investigator choice – histology dependent

Socinski et al. Ann Oncol 2016; 27 (suppl 6): abstr LBA7_PR

CheckMate 026: PFS in PD-L1+ ≥5%



	Nivolumab n=211	Chemotherapy n=212
Median PFS, months (95% CI)	**4.2** (3.0, 5.6)	**5.9** (5.4, 6.9)
1-year PFS rate, %	**23.6**	**23.2**

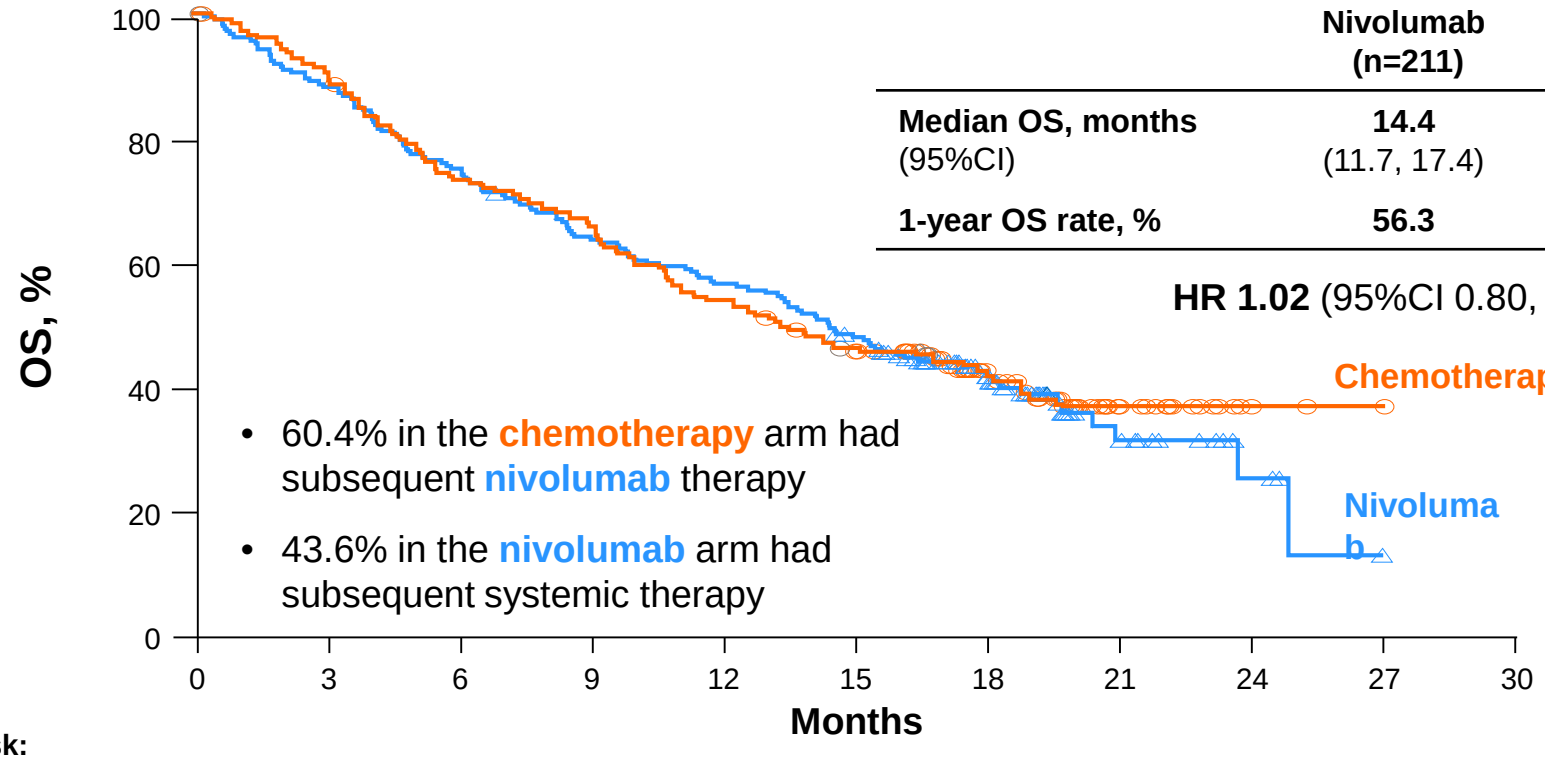
HR=1.15 (95% CI: 0.91, 1.45), ***P*=.2511**

No. of patients at risk:										
Nivolumab	211	104	71	49	35	24	6	3	1	0
Chemotherapy	212	144	74	47	28	21	8	1	0	0

All randomly assigned patients (≥1% PD-L1+): HR=1.17 (95% CI: 0.95, 1.43)

Socinski M, et al. ESMO 2016. Abstract LBA7_PR.

CheckMate 026: OS in PD-L1+ ≥5%



	Nivolumab (n=211)	Chemotherapy (n=212)
Median OS, months (95%CI)	**14.4** (11.7, 17.4)	**13.2** (10.7, 17.1)
1-year OS rate, %	**56.3**	**53.6**

HR 1.02 (95%CI 0.80, 1.30)

Number at risk:

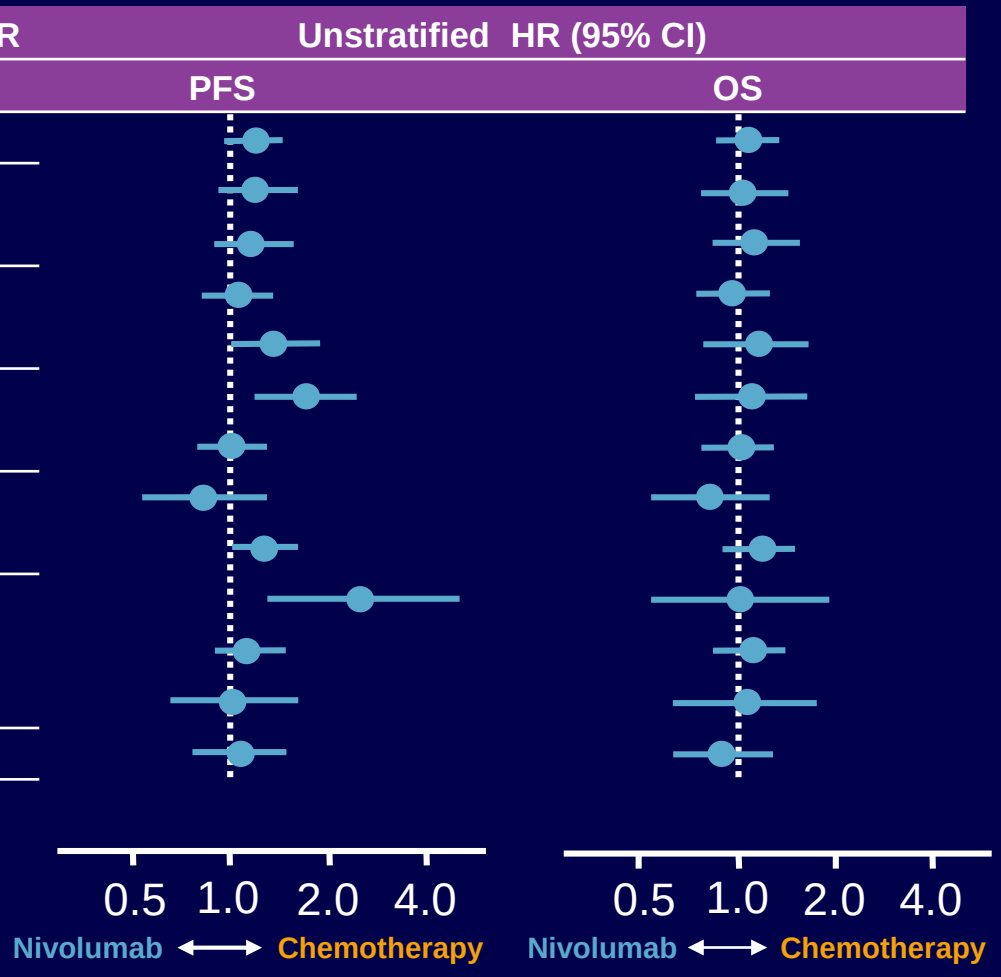
Nivolumab	211	186	156	133	118	98	49	14	4	0	0
Chemotherapy	212	186	153	137	112	91	50	15	3	1	0

All randomised patients (≥1% PD-L1+): HR 1.07 (95%CI 0.86, 1.33)

Socinski et al. Ann Oncol 2016; 27 (suppl 6): abstr LBA7_PR

CheckMate-026: Survival Outcomes by Subgroup

Subgroup	Pts, n		Unstratified HR	
	Nivolumab	Chemotherapy	PFS	OS
Overall	271	270	1.19	1.08
≥ 65 yrs	123	137	1.21	1.04
< 65 yrs	148	133	1.17	1.13
Male	184	148	1.05	0.97
Female	87	122	1.36	1.15
ECOG PS = 0	85	93	1.69	1.11
ECOG PS ≥1	185	177	1.01	1.02
Squamous	65	64	0.83	0.82
Nonsquamous	206	206	1.29	1.17
Never smoker	30	29	2.51	1.02
Former smoker	186	182	1.14	1.09
Current smoker	52	55	1.03	1.05
≥ 50% PD-L1+	88	126	1.07	0.90



Socinski M, et al. ESMO 2016. Abstract LBA7_PR.

Slide credit: clinicaloptions.com

CheckMate-026: Select Treatment-Related Adverse Events

Adverse Event, %	Nivolumab (n = 267)		Chemotherapy (n = 263)	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Any	71.2	17.6	92.4	50.6
Diarrhea	13.9	1.1	12.9	1.9
Fatigue	21.0	1.1	35.4	5.3
Nausea	11.6	0.4	48.3	1.9
Vomiting	5.6	0	22.8	1.9
Anemia	3.4	0.4	43.0	17.5
Neutropenia	0	0	18.3	11.0
Thrombocytopenia	0.7	0.4	14.4	8.4

Socinski M, et al. ESMO 2016. Abstract LBA7_PR.

Slide credit: clinicaloptions.com

BIRCH: Efficacy and Safety of Atezolizumab

	First Line (n = 139)	Second Line (n = 267)	≥ Third Line (n = 253)
Median OS, mos (95% CI)			
TC2/3 or IC2/3	14.0 (14.0-NE)	NE (11.2-NE)	NE (8.4-NE)
TC3 or IC3	NE (10.4-NE)	NE (10.6-NE)	NE (NE-NE)
6-mo OS, %			
TC2/3 or IC2/3	82	76	71
TC3 or IC3	79	80	75
Median PFS, mos (95% CI)			
TC2/3 or IC2/3	**5.5** (3.0-6.9)	2.8 (1.5-3.5)	2.8 (2.7-3.7)
TC3 or IC3	**5.5** (2.7-8.3)	4.1 (1.8-5.5)	4.2 (2.8-5.6)
6-mo PFS, %			
TC2/3 or IC2/3	46	29	31
TC3 or IC3	48	34	39

- Majority of AEs were grade 1/2 (80%)
- Most common AEs (any grade): fatigue, diarrhea and nausea
- Most common grade 3/4 AEs: pneumonitis* (1.5%), increased AST (0.8%), colitis (0.5%), hypothyroidism and rash (both 0.3%)

*1 grade 5 pneumonitis occurrence reported

Besse, et al. ECC 2015. Abstract 16LBA

Slide credit: clinicaloptions.com

JAVELIN: Phase Ib Trial of First-line Avelumab in NSCLC

- Open-label, dose-escalation phase Ib trial of avelumab (10 mg/kg Q2W) in advanced NSCLC not previously treated for metastatic disease

Outcome, %	N = 75
ORR	18.7
DCR	64.0
CR	1.3
PR	17.3
SD	45.3
Median PFS	**11.6 wks**

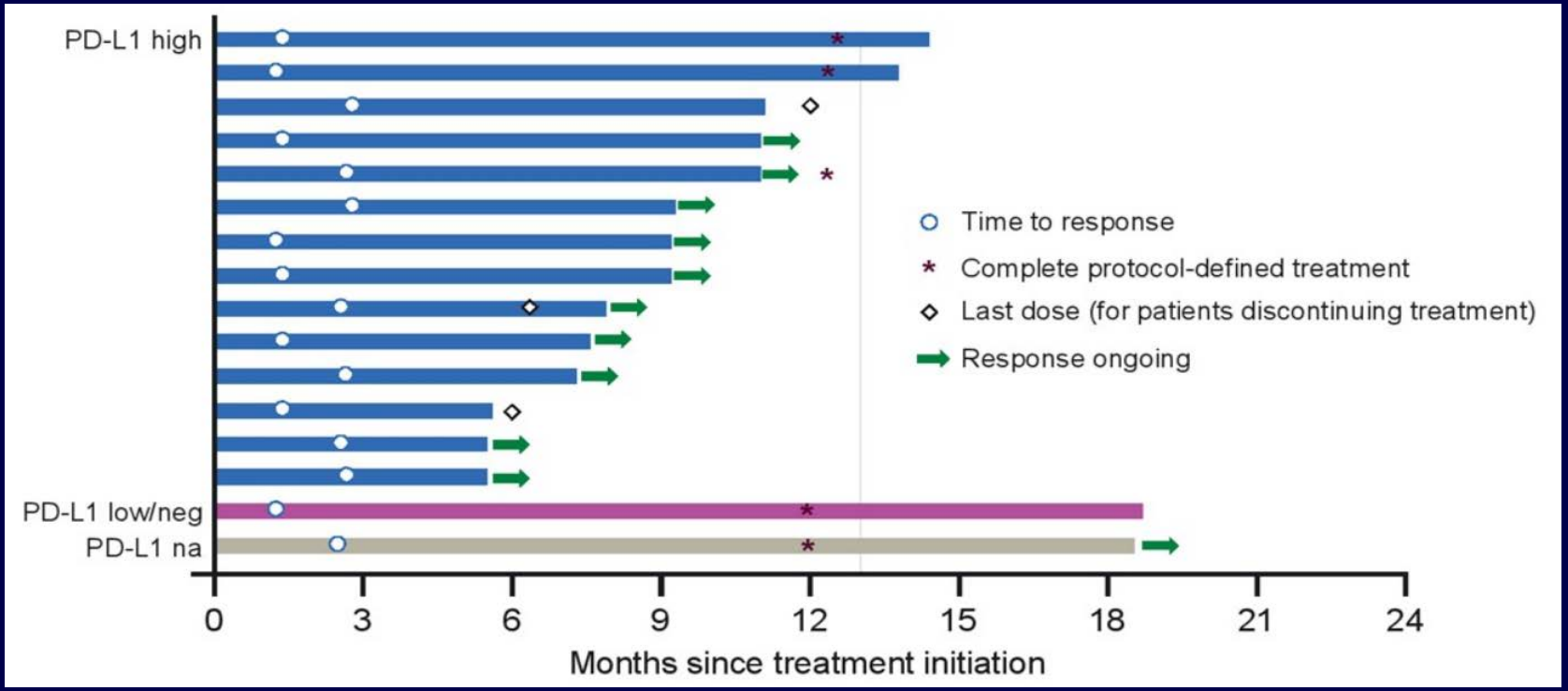
- Well tolerated, low rate of grade 3/4 AEs
- Tx-related AEs: 56.6% (9% grade 3/4)
- No tx-related deaths

Verschraegen CF, et al. ASCO 2016. Abstract 9036.

Slide credit: clinicaloptions.com

Phase I/II Trial of Durvalumab in Treatment-Naive Advanced NSCLC

- Dose-escalation/dose-expansion phase I/II trial of durvalumab (10 mg/kg Q2W) in pts with treatment-naive PD-L1+ NSCLC
- **ORR: 27%** (N = 59); 29% for PD-L1 high (n = 49); 11% for PD-L1 low or negative (n = 9)



Antonia SJ, et al. ASCO 2016. Abstract 9029.

Slide credit: clinicaloptions.com

PD-L1 IHC Assays

	Pembrolizumab* (Anti–PD-1)	Nivolumab* (Anti–PD-1)	Atezolizumab (Anti–PD-L1)	Durvalumab (Anti–PD-L1)
Diagnostic partner	Dako	Dako	Ventana	Ventana
Clone	22C3[1]	28-8[2]	SP142[3]	SP263
Machine utilized	Link 48	Link 48	BenchMark ULTRA	BenchMark ULTRA
Compartment	TC	TC	TC/IC	TC
Variables	% of cells	% of cells	% of cells	% of cells
Definition of positive	PD-L1(+): ≥ 50%	PD-L1(+): ≥ 1%	PD-L1(+): TC3/IC3 (≥ 50% / ≥ 10%) TC2/IC2 (5% - 49% / 5% - 9%) TC1/IC1 (1% - 4%)	PD-L1(+): ≥ 25%

*FDA-approved assays.

1. Garon EB, et al. N Engl J Med. 2015;372:2018-2028.
2. Phillips T, et al. Appl Immunohistochem Mol Morphol. 2015;23:541-549.
3. Fehrenbacher L, et al. Lancet. 2016;387:1837-1847.

Slide credit: clinicaloptions.com

IASLC

ORIGINAL ARTICLE

PD-L1 Immunohistochemistry Assays for Lung Cancer: Results from Phase 1 of the Blueprint PD-L1 IHC Assay Comparison Project

CrossMark

Agent	Nivolumab	Pembrolizumab	Atezolizumab	Durvalumab
Primary antibody clone used in the assay system	28-8 (Dako)	22C3 (Dako)	SP142 (Ventana)	SP263 (Ventana)
Interpretive scoring	Tumor cell membrane	Tumor cell membrane	Tumor cell membrane Infiltrating immune cells	Tumor cell membrane
Instrument and detection systems required	EnVision Flex on AutostainerLink 48	EnVision Flex on AutostainerLink 48	OptiView detection and amplification on Benchmark ULTRA	OptiView detection on Benchmark ULTRA
Therapeutic developer	Bristol-Myers Squibb	Merck	Genentech	AstraZeneca

PD-L1, programmed death ligand 1.

Hirsch, JTO 2017

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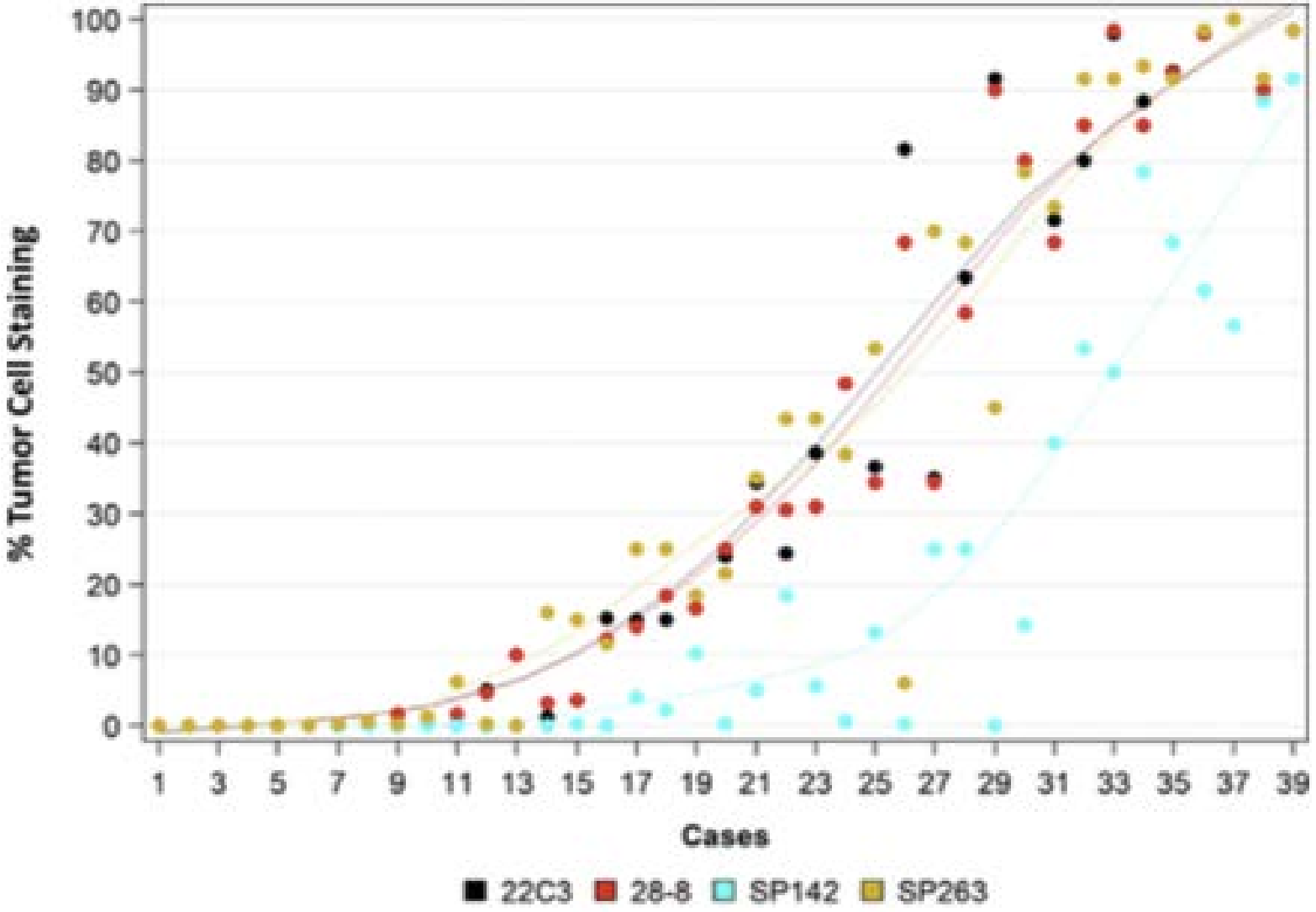
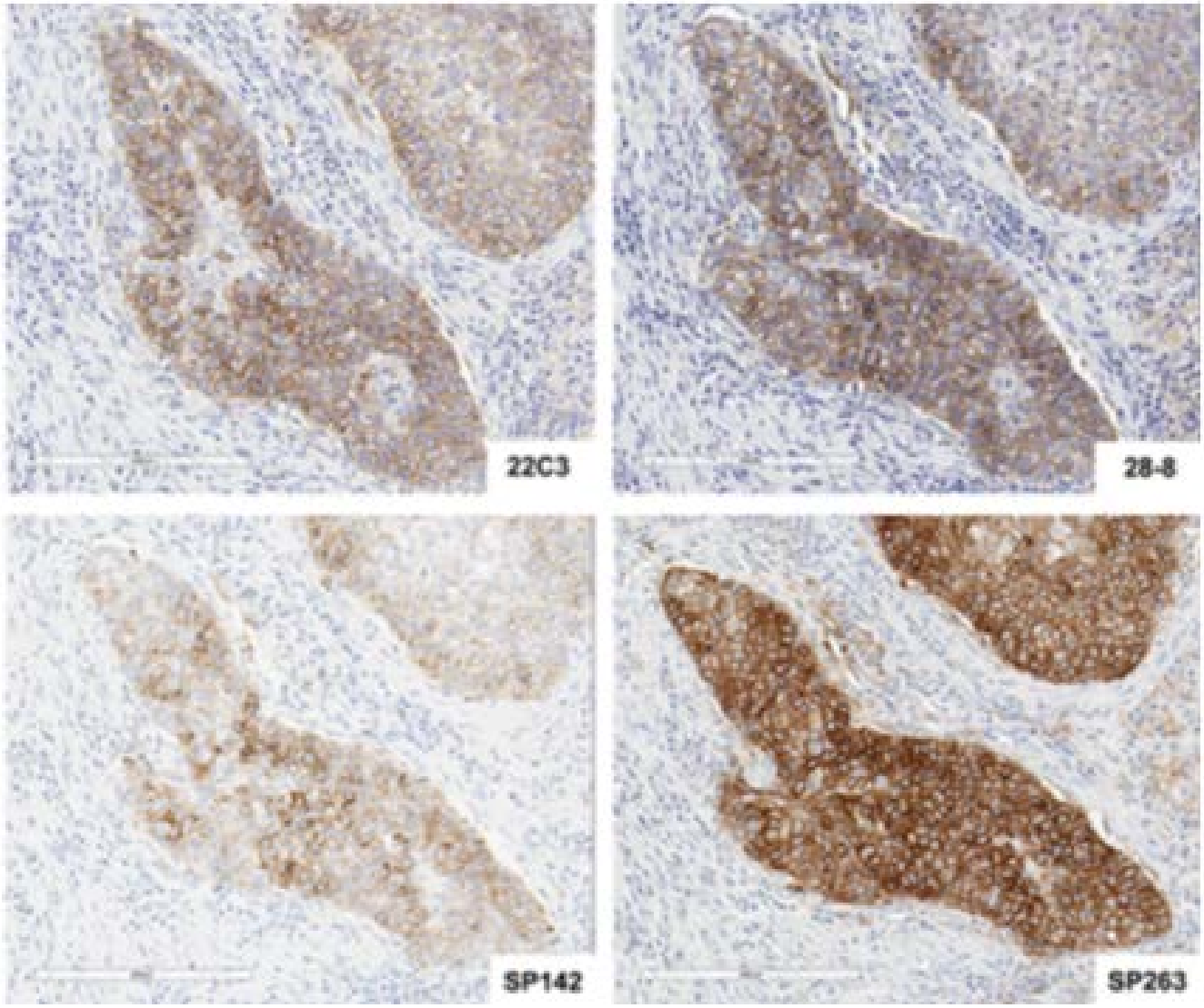
PD-L1 staining: comparison of 4 antibodies



Hirsch, JTO 2017

PD-L1 staining: comparison of 4 antibodies



Hirsch, JTO 2017

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Medscape Medical News > Conference News

Pembrolizumab First-Line Beats Chemo: 'It's a New Day for Lung Cancer'

Zosia Chustecka

October 09, 201

Medsc

Ear

Zosia

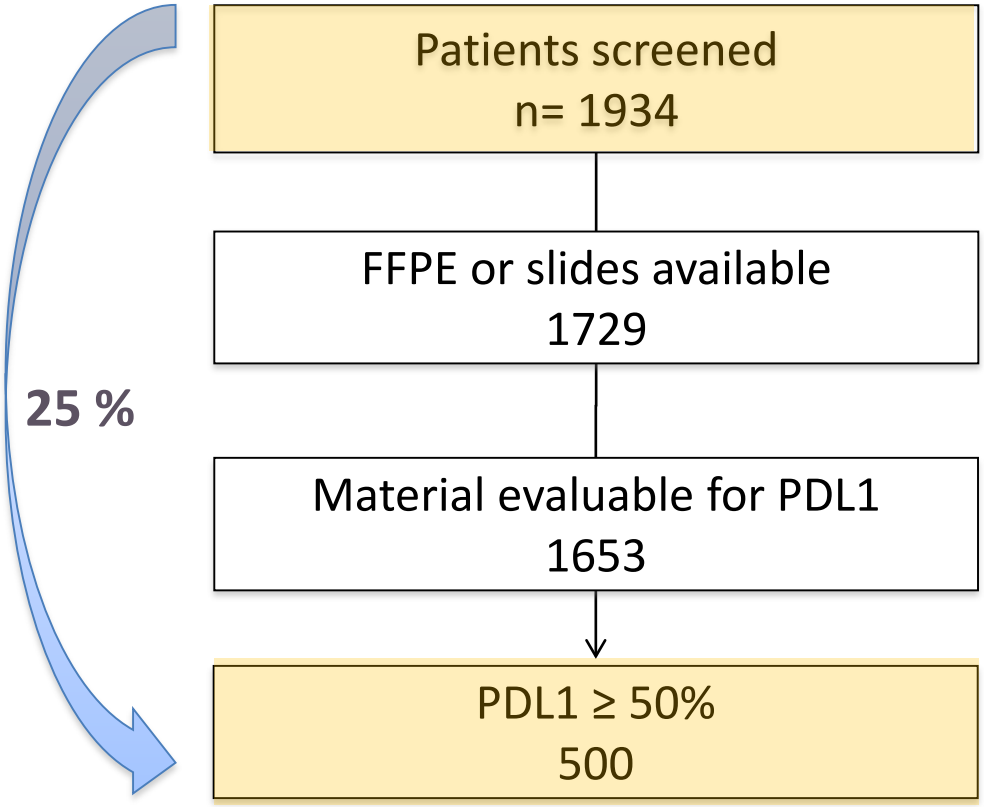
Octob

R.it | OncoLine - Il canale di Oncologia

News | Prevenzione | Diagnosi | Terapia | Diritti | Qualità di vita | Testimonianze

Il polmone sotto attacco, il cancro si può abbattere con l'immunoterapia

Putting data in context



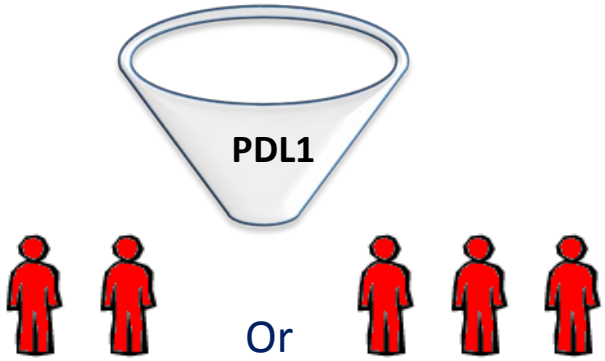
- EGFR mutant or ALK translocated NSCLC
  15-20% of Caucasians
  40-50% of Asians
- PS ≥ 2 is reported in ~34% of contemporary cohorts of NSCLC patients
- European FRAME study (1 500 pts)
  17% of pts have brain mets at diagnosis
  34% of them have radiotherapy before CT
- Autoimmune disorders affect 5 to 9% of the general population and 14% of NSCLC

Barlesi F et al, Lancet. 2016 Moro-Sibilot D et al, Lung Cancer 2015; 90: 427 Khan SA et al, JAMA Oncol 2016; 1-2 Salloum RG al, Cancer 2011, 117: 1038

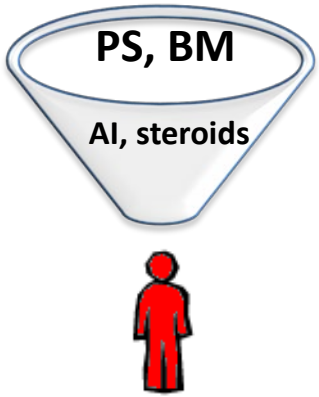
Adapted from Soria, ESMO 2016

Putting data in context

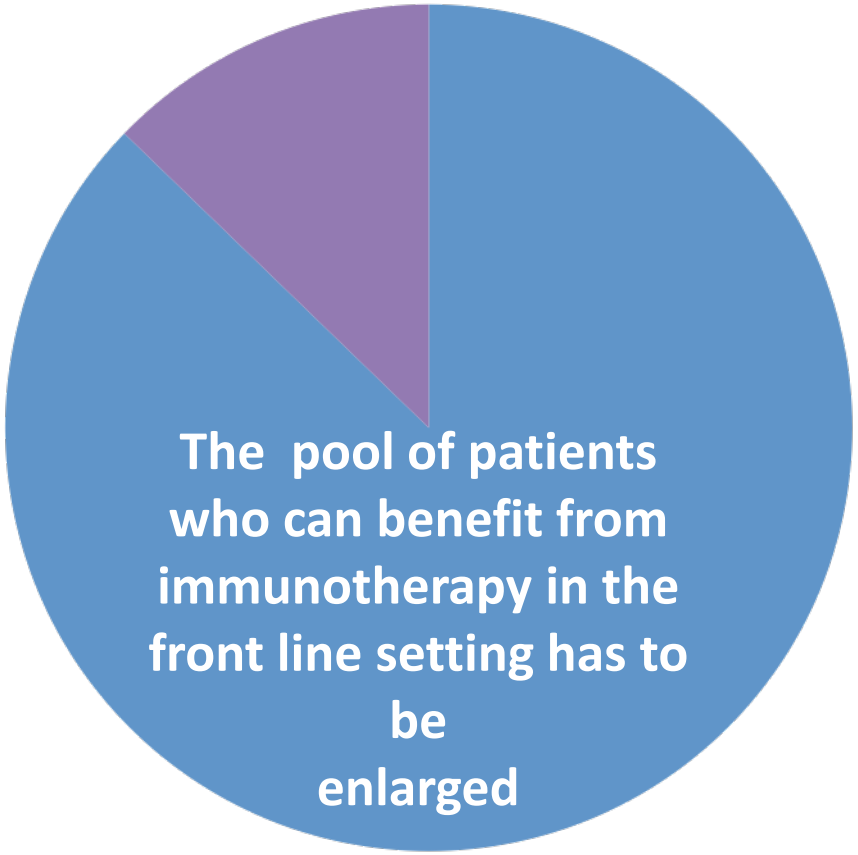
NSCLC patients in daily practice



NSCLC patients with PDL1 ≥ 50%



PS 0/1, no untreated BM, no AI, no steroids

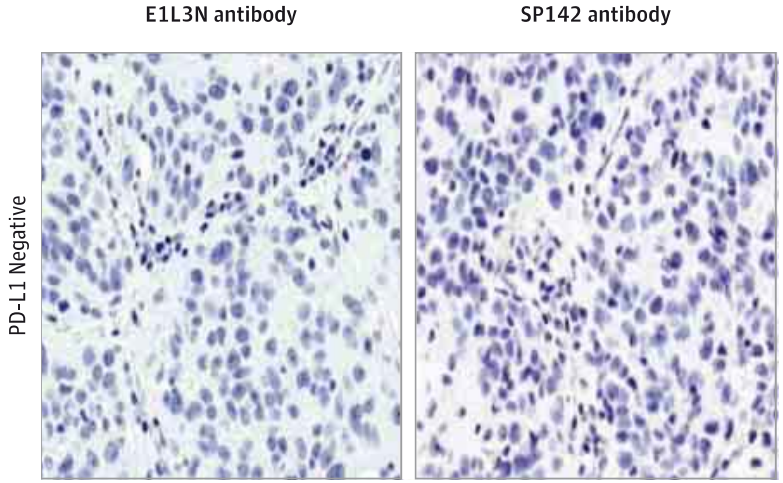


Soria, ESMO 2016

How to enlarge the pool of patients eliglible to first-line immunotherapy?

- **Make sure our patient is not PD-L1 negative**
- **Identify other predictors of benefit**
- **Explore novel combinations**

PD-L1 expression: intratumoral heterogeneity in resected NSCLC

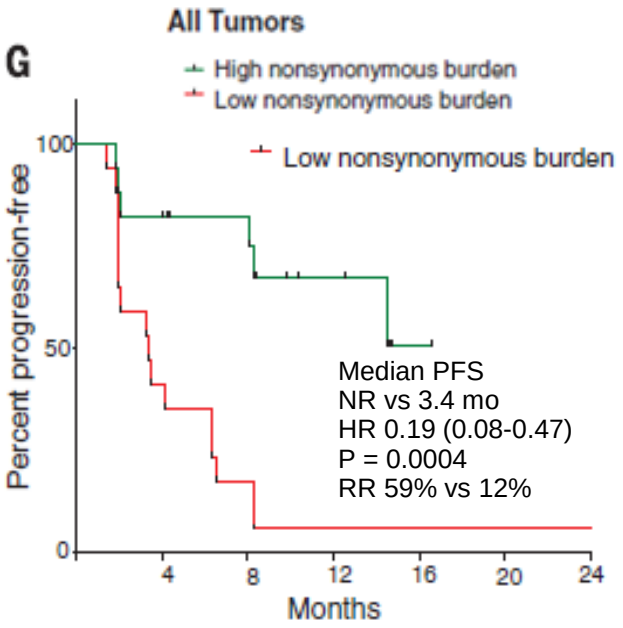


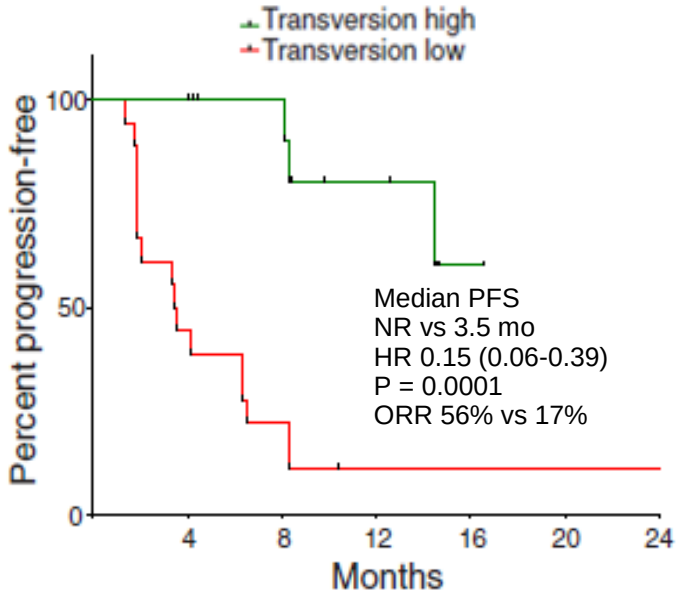
N=49

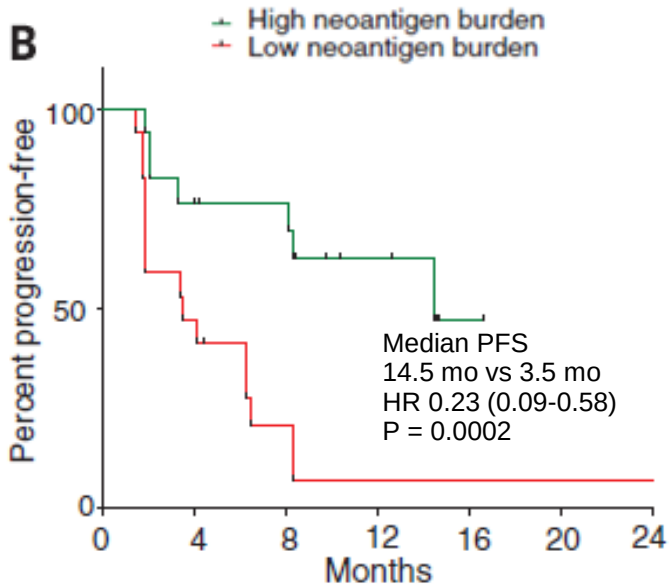
McLaughlin, JAMA Oncol 2015

- **Make sure our patient is not PD-L1 negative**
- **Identify other predictors of benefit**
- **Explore novel combinations**

Mutational burden and pembrolizumab activity







Rizvi NA et al. Science 348:124-8, 2015

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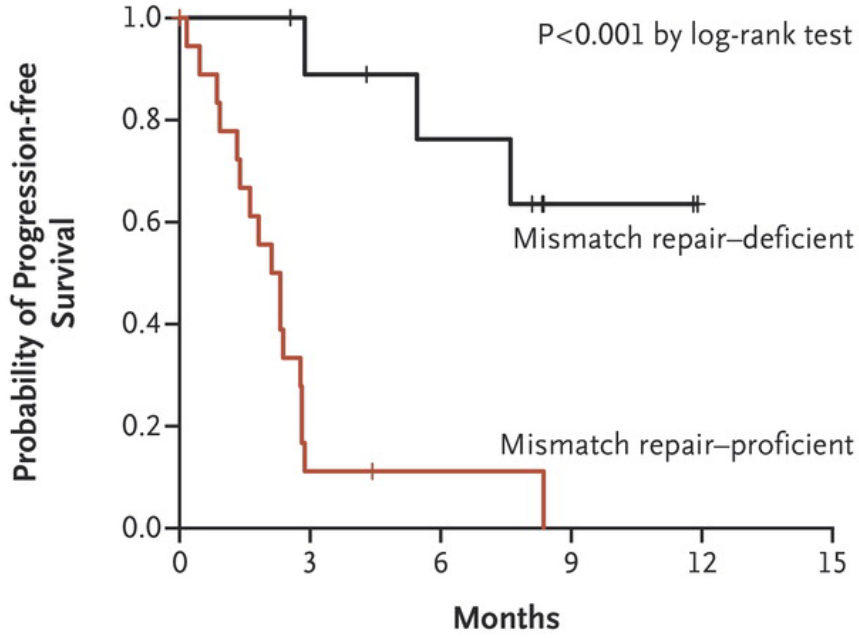
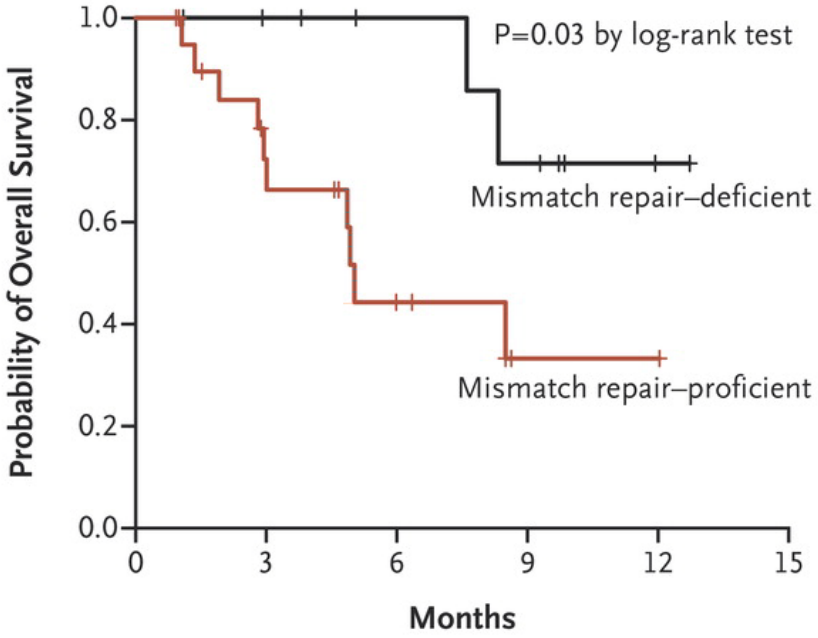
Mismatch-repair status predics clinical benefit from pembrolizumab in CRC

A Progression-free Survival in Cohorts with Colorectal Cancer



No. at Risk						
Mismatch repair–deficient	11	8	6	2	0	0
Mismatch repair–proficient	21	2	1	0	0	0

B Overall Survival in Cohorts with Colorectal Cancer

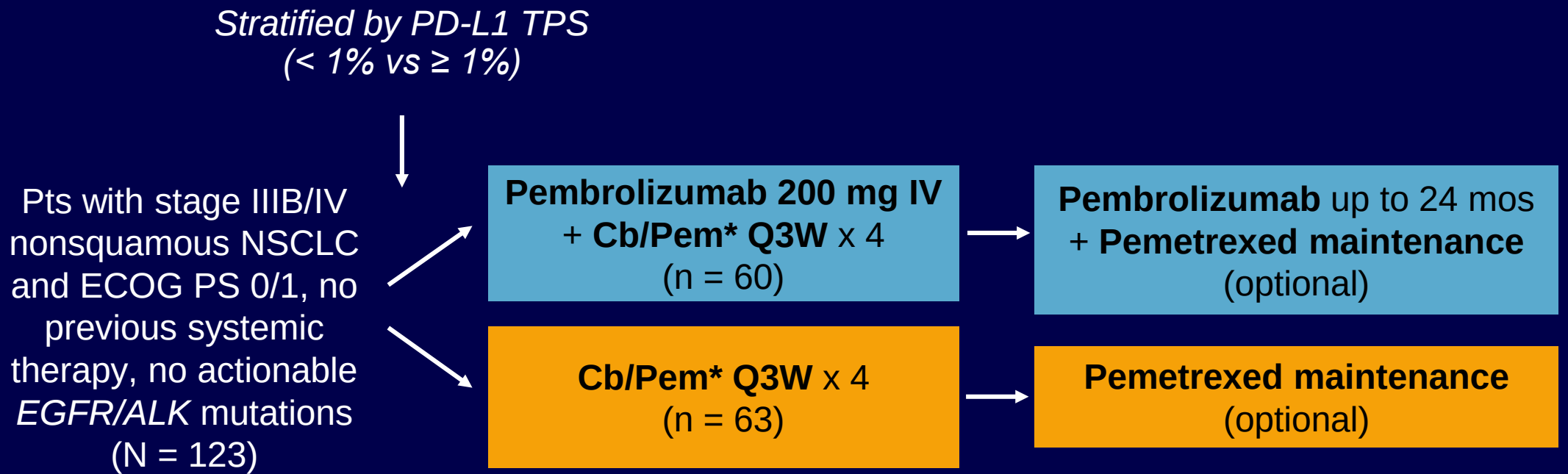


No. at Risk						
Mismatch repair–deficient	11	9	7	5	1	0
Mismatch repair–proficient	21	12	5	1	1	0

Le, NEJM 2015

- **Make sure our patient is not PD-L1 negative**
- **Identify other predictors of benefit**
- **Explore novel combinations**

Pembrolizumab + CT as First-line Therapy for Adv Nonsq NSCLC (KEYNOTE-021)



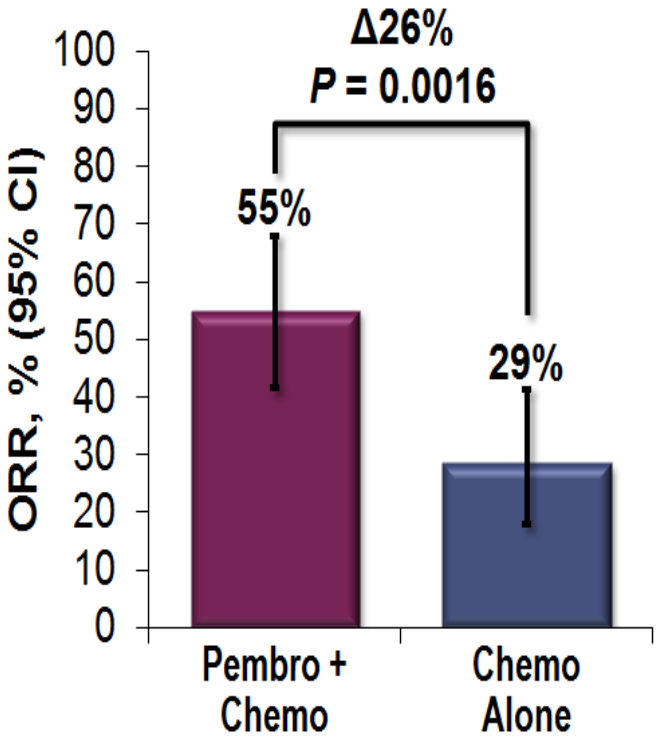
*Cb AUC 5 mg/mL/min; Pem 500 mg/m^2.

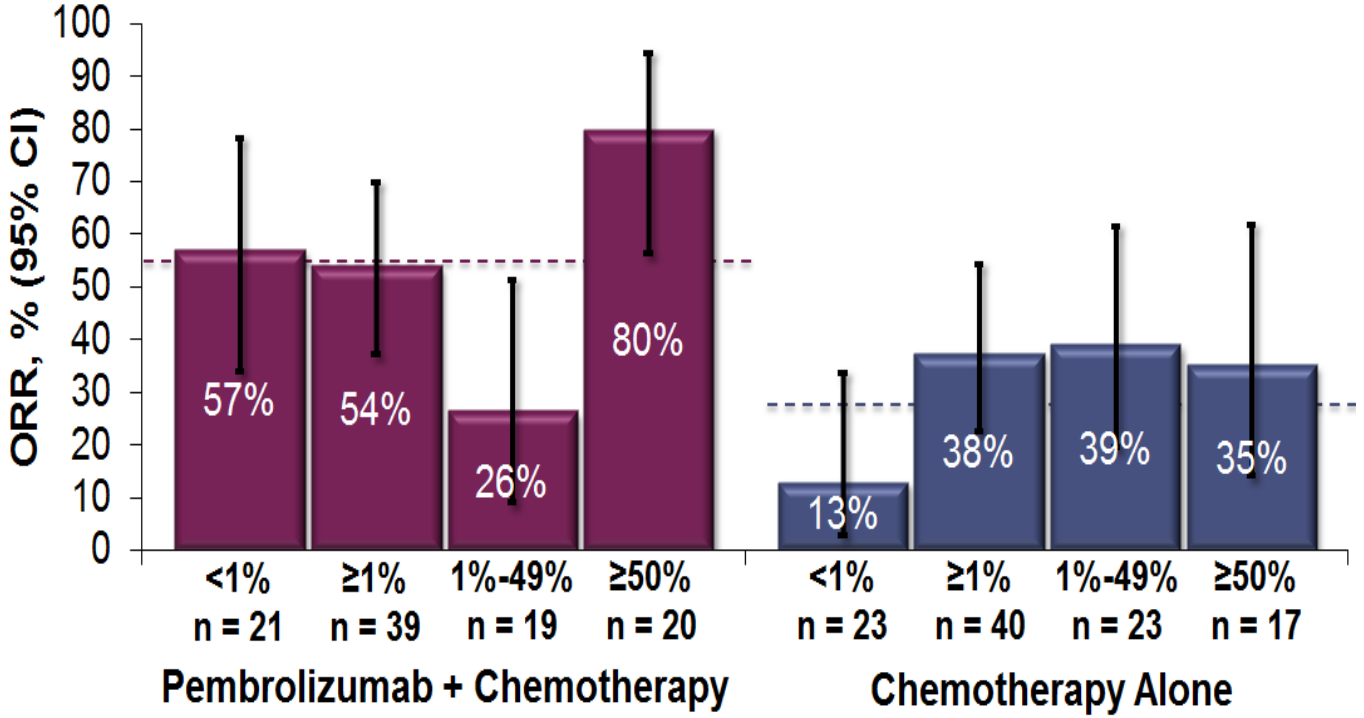
- Primary endpoint: ORR (RECIST v1.1)
- Secondary endpoints included: PFS, DoR, OS, and safety

Langer C, et al. Lancet Oncol. 2016;[Epub ahead of print].

Slide credit: clinicaloptions.com

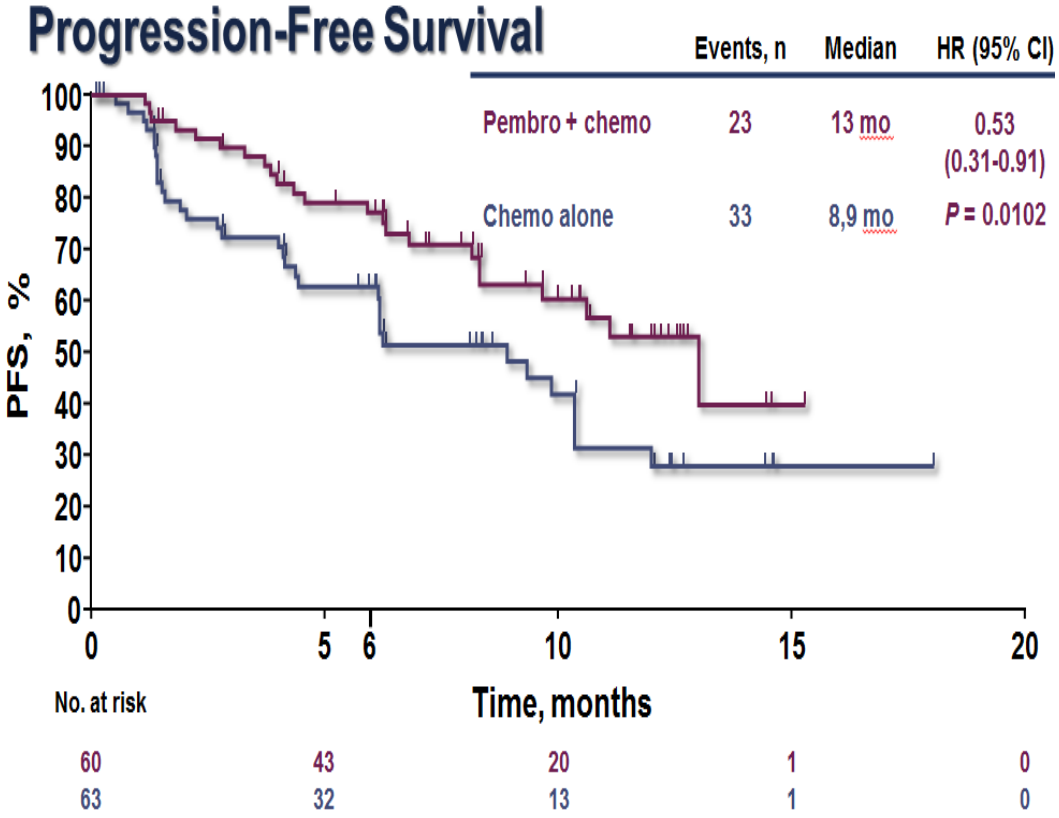
Keynote 021 cohort G: response rate

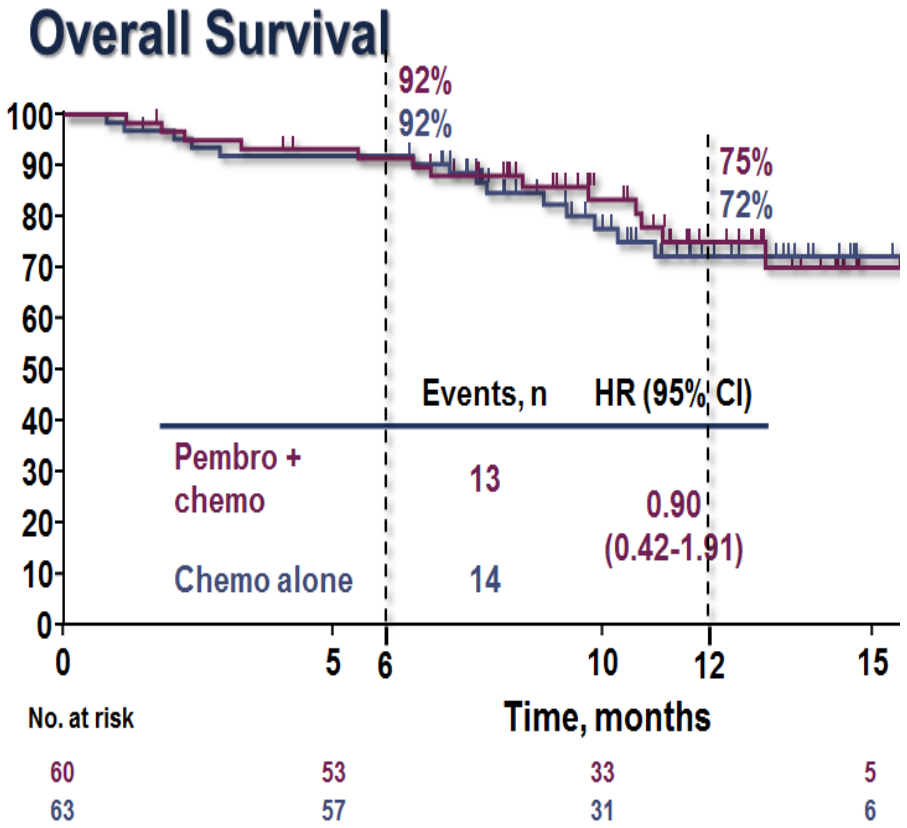




Langer, ESMO 2016

Keynote 021 cohort G: PFS and OS





Langer, ESMO 2016

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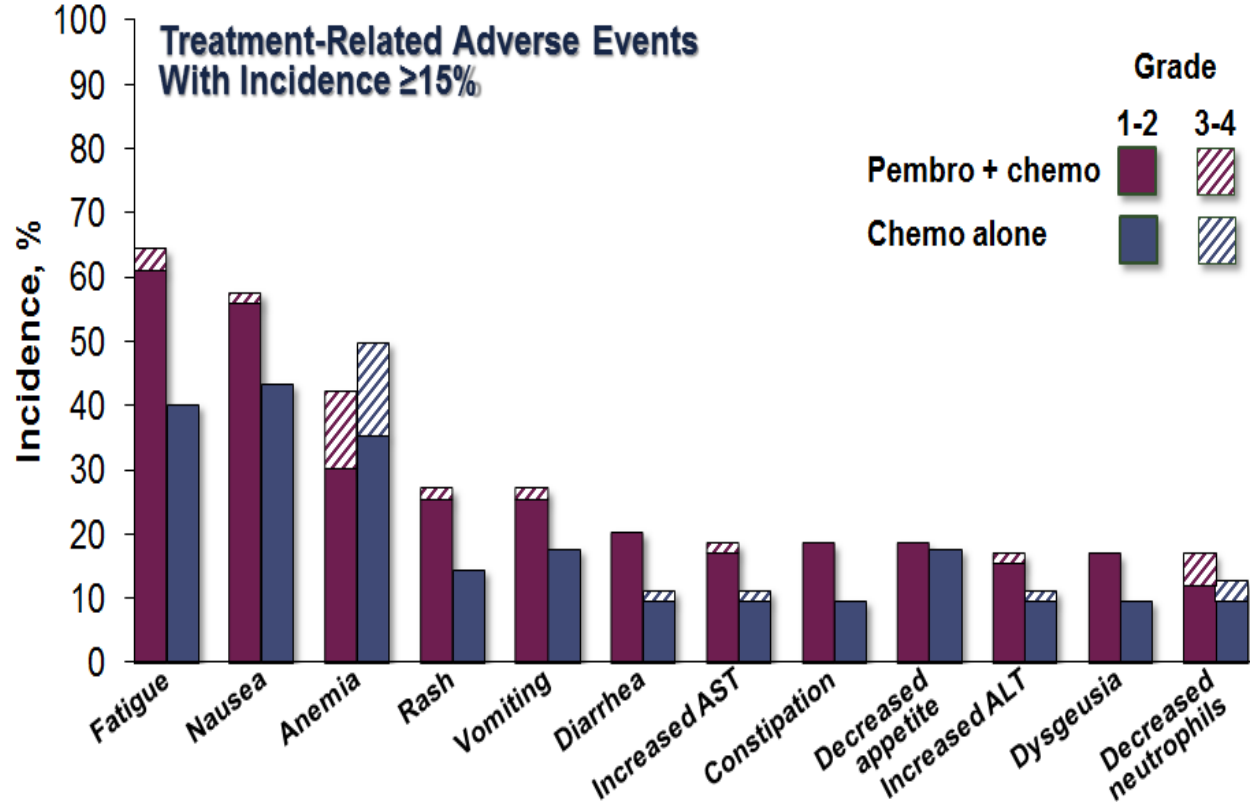
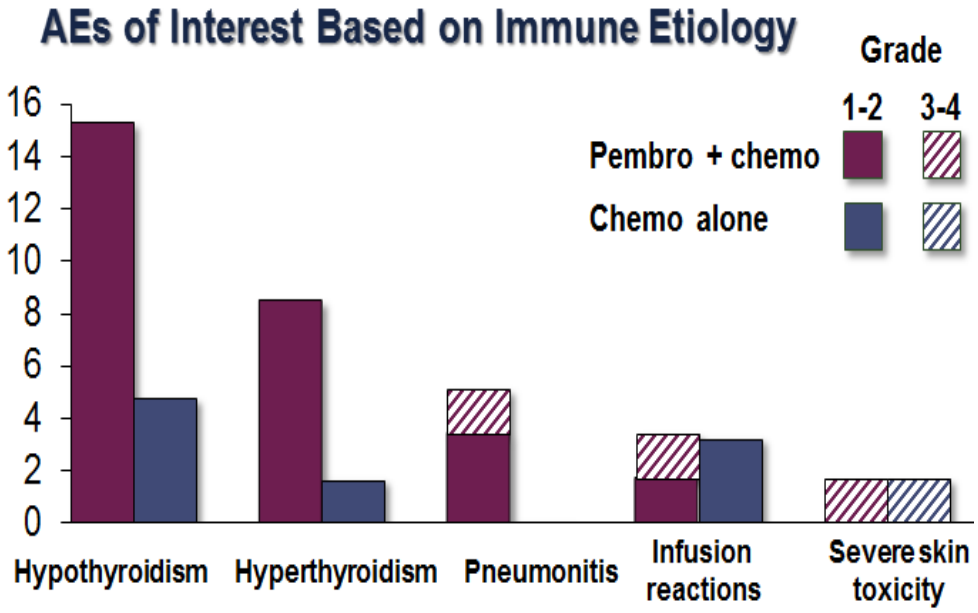
Toxicity





- Pembrolizumab + chemotherapy combination lead to a:
  - ✓ Numerical increase of many chemo-related AEs
  - ✓ Typical checkpoint inhibitors immune-mediate AEs
  - ✓ An Overall G3/4 AE rate of 39% (combo) vs 26% (CT)

Adapted from Soria, ESMO 2016

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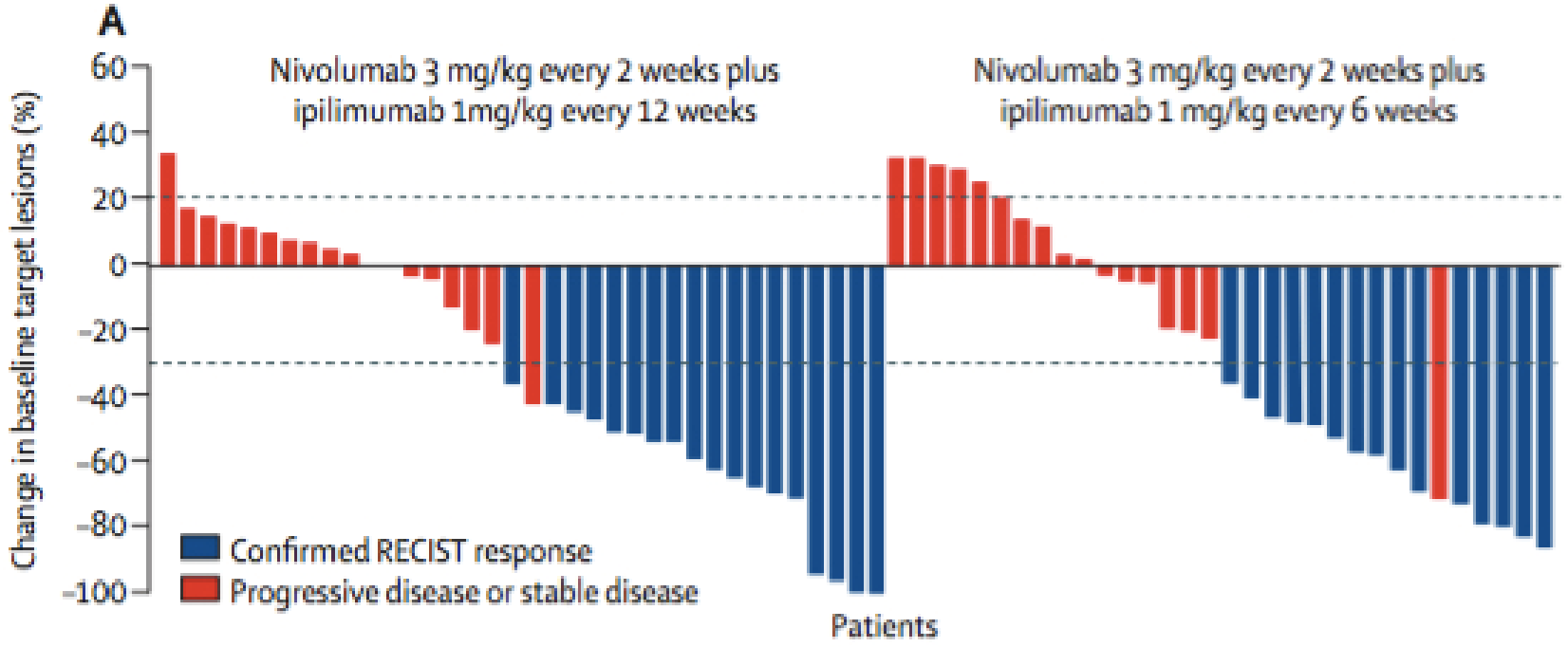
Nivolumab plus ipilimumab as first-line treatment for advanced non-small-cell lung cancer (CheckMate 012): results of an open-label, phase 1, multicohort study

Matthew D Hellmann, Naiyer A Rizvi, Jonathan W Goldman, Scott N Gettinger, Hossein Borghaei, Julie R Brahmer, Neal E Ready, David E Gerber, Laura Q Chow, Rosalyn A Juergens, Frances A Shepherd, Scott A Laurie, William J Geese, Shruti Agrawal, Tina C Young, Xuemei Li, Scott J Antonia

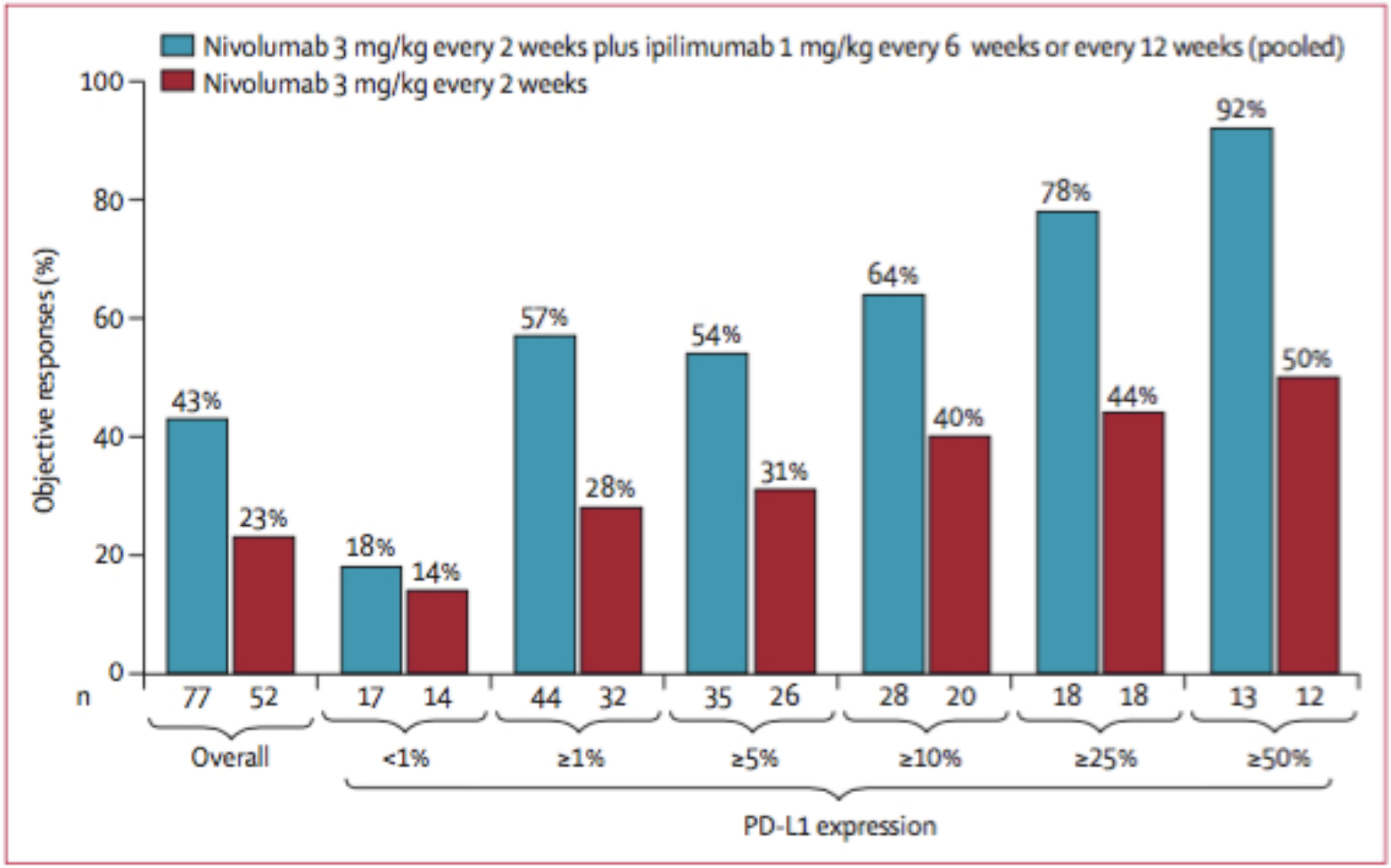


RR 47%

RR 38%

Lancet 2017

PD-L1 levels predict benefit (RR) from nivo + ipi



Hellmann, Lancet Oncology 2017

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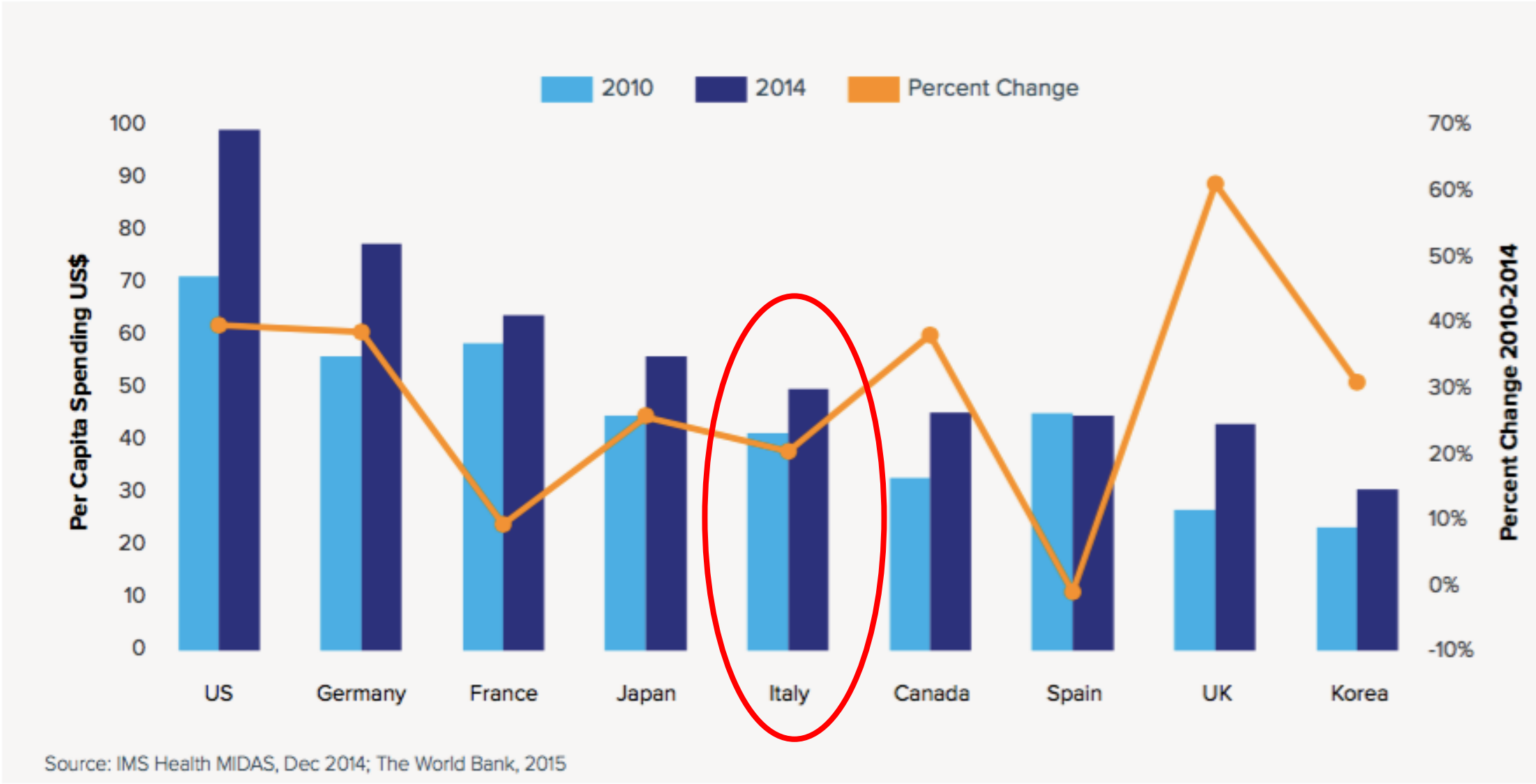
Therapeutic Oncology Drug Spend Per Capita 2010–14



Source: IMS Health MIDAS, Dec 2014; The World Bank, 2015

Global Oncology Trend Report 2015– IMS Health

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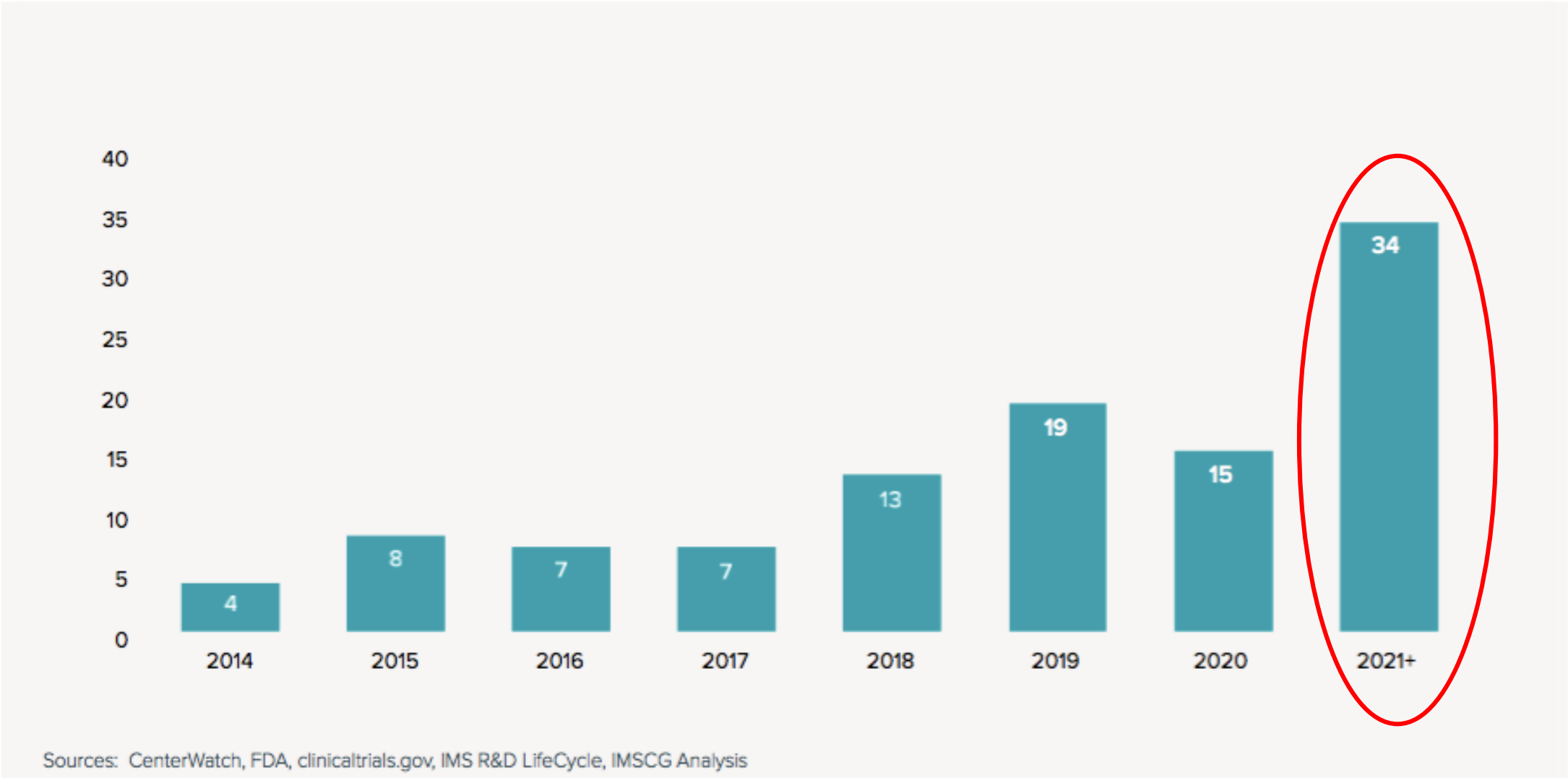
Expected Combination Regimen Launches in Oncology



Global Oncology Trend Report 2015– IMS Health

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ESMO European Consortium Study on the availability, out-of-pocket costs and accessibility of antineoplastic medicines in Europe

N. Cherny[1*], R. Sullivan[2], J. Torode[3], M. Saar[4] & A. Eniu[5]

Conclusions: The cost and affordability of anticancer treatments with recent market approval is the major factor contributing to inequity of access to anticancer medications. This is especially true with regards to new medications used in the management of EGFR- or ALK-mutated non-small-cell lung cancer, metastatic melanoma, metastatic renal cell cancer, RAS/RAF wild-type metastatic colorectal cancer, HER2 overexpressed breast cancer and castration-resistant metastatic prostate cancer.

"If companies work with us to price drugs reasonably and manage any uncertainties in the evidence base, we can continue to recommend patients have routine access to the treatments they need."

Professor Carole Longson, director of the NICE centre for health technology evaluation

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Presidenza del Consiglio dei Ministri

CNB
COMITATO NAZIONALE
PER LA BIOETICA

MOZIONE

PER UNA POLITICA DI ACCESSO EQUO A FARMACI INNOVATIVI AD ALTA EFFICACIA PER PATOLOGIE GRAVI: RIDUZIONE DEI PREZZI E CONTENIMENTO DEI COSTI A CARICO DEL SSN E DEI CITTADINI[1]

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Presidenza del Consiglio dei Ministri

CNB
COMITATO NAZIONALE
PER LA BIOETICA

[...] pur comprendendo che occorre evitare di porre un freno agli incentivi per l'innovazione farmaceutica, richiama l'esigenza di **limitare gli eccessi di una ricerca esagerata del profitto** in un settore, quello della salute, che dovrebbe essere governato dal sistema pubblico in modo molto più incisivo, trasparente ed equo. È allora indispensabile **individuare un prezzo adeguato dei farmaci rispetto ai costi sostenuti per la ricerca** (tra l'altro spesso finanziata con denaro pubblico o acquisita da piccole industrie biotecnologiche) e per la commercializzazione.

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OncoLine - Il canale di Oncologia

News | Prevenzione | Diagnosi | Terapia | Diritti | Qualità di vita | Testimonianze

Il polmone sotto attacco, il cancro si può abbattere con l'immunoterapia

Patients expectations?

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JAMA Oncology | Original Investigation

Determinants of Patient-Oncologist Prognostic Discordance in Advanced Cancer

Robert Gramling, MD, DSc; Kevin Fiscella, MD, MPH; Guibo Xing, PhD; Michael Hoerger, PhD; Paul Duberstein, PhD; Sandy Plumb, BS; Supriya Mohile, MD, MS; Joshua J. Fenton, MD, MPH; Daniel J. Tancredi, PhD; Richard L. Kravitz, MD, MSPH; Ronald M. Epstein, MD

RESULTS Among the 236 patients (mean [SD] age, 64.5 [11.4] years; 54% female), 161 patient-oncologist survival prognosis ratings (68%; 95% CI, 62%-75%) were discordant. Discordance was substantially more common among nonwhite patients compared with white patients (95% [95% CI, 86%-100%] vs 65% [95% CI, 58%-73%], respectively; $P = .03$). Among 161 discordant patients, 144 (89%) did not know that their opinions differed from that of their oncologists and nearly all of them (155 of 161 [96%]) were more optimistic than their oncologists.

JAMA Oncology 2016

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JAMA Oncology | Original Investigation

Effect of a Patient-Centered Communication Intervention on Oncologist-Patient Communication, Quality of Life, and Health Care Utilization in Advanced Cancer

The VOICE Randomized Clinical Trial

INTERVENTIONS Oncologists received individualized communication training using standardized patient instructors while patients received question prompt lists and individualized communication coaching to identify issues to address during an upcoming oncologist visit. Both interventions focused on *engaging* patients in consultations, *responding* to emotions, *informing* patients about prognosis and treatment choices, and *balanced framing* of information. Control participants received no training.

RESULTS Data from 38 oncologists (19 randomized to intervention) and 265 patients (130 intervention) were analyzed. In fully adjusted models, the intervention resulted in clinically and statistically significant improvements in the primary physician-patient communication end point (adjusted intervention effect, 0.34; 95% CI, 0.06-0.62; $P = .02$). Differences in secondary outcomes were not statistically significant.

Epstein, JAMA Oncology 2016

Mi sono presa del tempo per riflettere, pensare ed **elaborare un po' il mio dispiacere**, ma ora sono pronta per iniziare la nuova terapia che mi avete proposto.

Sinceramente vorrei iniziare appena possibile, ho già **parlato con mia figlia** e con il parrucchiere per la rasatura, la parrucca, i cappellini ed i foulard... Anzi se avete suggerimenti, indirizzi, contatti...!

Ho iniziato a frequentare una palestra con una personal trainer **molto dinamica e sensibile**, male non fa al sistema immunitario, vero?

Ho la testa in fibrillazione, ho ancora molti sogni e tanta fede.

Non arrendetevi e lottate con me, datemi coraggio, dobbiamo proprio farcela!!!

LUCE network pone al centro la passione e lo spirito di servizio
degli oncologi italiani con l'obiettivo comune di offrire valore ai pazienti

Lung Cancer LUCE Center Network

LUCE network è una community of practice rivolta agli specialisti per promuovere sinergie nella gestione efficiente dei pazienti con neoplasie toraco-polmonari

Appartenere al network significa aprirsi al confronto, aumentare l'impatto dei programmi di ricerca e investire nel nostro presente e futuro

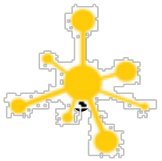
per richiedere l'iscrizione: www.lucenetwork.it

LUCE

Fare ricerca vuol dire offrire migliori opzioni terapeutiche ai nostri Pazienti

In LUCE network i Trial attivi sono facilmente consultabili per

- istotipo
- target
- linea di trattamento



Center Net (protocolli attivi per ospedale)

Clinical Trial ongoing (NSCLC, SCLC, MPM e Timoma)

Forum di discussione

per richiedere l'iscrizione: www.lucenetwork.it

Mobile Interaction

per richiedere l’iscrizione: www.lucenetwork.it